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Use of Antimicrobials in a Tertiary Children's Hospital



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USE OF ANTIMICROBIALS IN A TERTIARY CHILDREN'S HOSPITAL

Niina Laine

ACADEMIC DISSERTATION

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ABSTRACT

BACKGROUND AND OBJECTIVES

Rational use of antimicrobials is paramount due to increasing bacterial resistance and a lack of novel antimicrobials. Investigating the clinical use and consumption of antimicrobials aids in the prudent use of these drugs in a tertiary paediatric hospital. The purpose of this study was to obtain detailed information on the use of antimicrobials in a tertiary Children's Hospital, Helsinki University Hospital (HUCH), in order to support prudent, safe and efficient use of antimicrobials. The consumption of antimicrobials and the quality and appropriateness of antimicrobial therapy (AMT) was investigated at the hospital level as well as in individual patient cases. The objectives were the following: 1) To evaluate the appropriateness of AMT in children with blood culture positive infections (Study I), 2) To investigate the consumption of antimicrobials in the hospital in Defined Daily Doses (Study II), 3) To record the prevalence of off-label (OL) use of antimicrobials in neonates (Study III) and last, 4) To analyse the occurrence of antimicrobial medication errors in children (Study IV).

MATERIALS AND METHODS

The Children's Hospital, University of Helsinki, is a tertiary hospital in Finland. Its departments include general paediatrics, paediatric surgery, oncology, transplantation and both paediatric and neonatal intensive care units (PICU, NICU). The hospital has approximately 130 beds. The average annual number of patient days is approximately 30,000 days.

Two of the studies involved individual patients. In Study I, data on 149 children (0–17 years) with blood culture positive hospital infections between 2005 and 2012 were collected. An expert panel evaluated the appropriateness of the targeted AMT. In Study III, the prevalence of OL use of antimicrobials was investigated in three different paediatric cohorts. The largest cohort consisted of premature NICU patients (450–2000g) with blood culture positive infections and antimicrobial therapy given between 2005 and 2014 (N=282). Overall, different types of methods were used regarding quantitative and qualitative analysis and retrospective reviews of electronic patient records and data.

Studies II and IV were registry studies. In Study II, the consumption of antimicrobials in Defined Daily Doses (DDDs according to the Anatomical Therapeutic Chemical (ATC)/DDD index) was investigated retrospectively between 2003 and 2013. In Study IV, the types of antimicrobial errors were analysed. The errors were reported by healthcare professionals using a voluntary web-based error reporting system, HaiPro. The data were obtained between June 2009 and December 2014 from four different medical wards. The majority of the studies were conducted retrospectively. Analysis of the studies was both quantitative and qualitative.

RESULTS

The AMT was inappropriate in 17% (26/149) of patients with blood culture positive infections (Study I). Three of these patients received antimicrobials that were totally ineffective according to *in vitro* data. Suboptimal or overly broad-spectrum AMT was administered to 13/26 (50%) patients. Increased bacterial resistance was likewise discovered. The use of certain anti-*Pseudomonas* antimicrobials, such as carbapenems, piperacillin tazobactam and ceftazidime, has increased notably during 11 years (Study II). During 2003 and 2013, the use of many beta-lactam antimicrobials increased. The most notable change was in the use of carbapenems, which increased by 110% during the study period. In the Children's Hospital, OL use of antimicrobials is relatively common. In NICU, 35% (7/20) of consumed antimicrobials were off-label in neonates between 2009 and 2014 (Study III). A total of 18% (51/282) of premature neonates with blood culture positive infection received at least one OL antimicrobial. An increase in birth weight was found to statistically significantly decrease the probability of OL usage (odds ratio=0.85 for 100g increase in birth weight, p-value < 0.001). Medication errors likewise compromised patient care and safety. In Study IV, there were 157 antimicrobial errors reported in 149 patients from four wards (GEN, NICU, HEM-ONC and INF). The majority of the reported errors (125/149, 84%) reached the patient. No fatal errors occurred. Two errors were reported as clinically significant (2/149, 1%). Most of the errors occurred with drugs with high consumption, such as cefuroxime (15/157, 10%) and penicillin G (15/157, 10%). Omission errors were the typical error with antimicrobials (37/149, 25%). The results from Studies I–IV further confirm multiple problems regarding the issues of declining paediatric medication safety and increasing antimicrobial resistance.

CONCLUSIONS

These studies gave a useful overall picture regarding AMT and the use of antimicrobials at the Children's Hospital. More attention should be paid to appropriate AMT, and training of prescribers should be provided. The increased use of carbapenems highlights constantly increasing microbial resistance. With premature neonates, the smaller the birth weight was, the higher the risk of OL antimicrobial use. Fortunately, antimicrobial medication errors were infrequently harmful to patients. This thesis provides a window into issues that undermine the quality of care regarding hospital infections in paediatrics and aids the launch of an antimicrobial stewardship program (ASP) in the Children's Hospital.

Keywords: antibacterial, antibiotic, antifungal, antimicrobial, antimicrobial stewardship program, antiviral, appropriate use, bacteria, blood culture positive infection, bloodstream infections (BSI), children, children's hospital, defined daily doses (DDDs), infectious diseases, label use, medication error, medication safety, neonatal intensive care unit (NICU), neonate, off-label use, pathogen, paediatric, paediatrics intensive care unit (PICU), paediatric, sepsis

TIIVISTELMÄ

TAUSTA JA TAVOITTEET

Mikrobilääkkeiden rationaalinen käyttö on tärkeää. Mikrobilääkeresistenssi kasvaa jatkuvasti ja uusia mikrobilääkkeitä ei ole riittävästi. Mikrobilääkkeiden asianmukaista käyttöä tertiäärisessä lastensairaalassa tukee klinisen käytön ja kulutuksen tutkiminen.

Tämän väitöstyön tavoite oli saada yksityiskohtaista tietoa mikrobilääkkeiden käytöstä tertiäärisessä lastensairaalassa (HUS), jotta voidaan tukea rationaalista, turvallista ja tehokasta mikrobilääkkeiden käyttöä. Mikrobilääkkeiden kulutus ja mikrobilääkehoidon laatu ja oikeellisuus tutkittiin sairaalatasolla sekä potilastapauksilla. Väitöstyön tavoitteet olivat seuraavat: 1) Arvioida mikrobilääkehoidon oikeellisuus lapsilla, jotka saivat mikrobilääkehoitoa veriviljelypositiivisiin infektioihin (Osatutkimus 1.), 2) Tutkia mikrobilääkkeiden kulutus sairaalassa käyttäen DDD-lukuja (Defined Daily Doses) (Osatutkimus 2.), 3) Tutkia ei-rekisteröityjen mikrobilääkkeiden käytön prevalenssia vastasyntyneillä (Osatutkimus 3.), 4) Analysoida sattuneet mikrobilääkehoitoon liittyneet lääkityspoikkeamat lapsilla (Osatutkimus 4.).

MATERIAALIT JA METODIT

Lastenkliniikka, Helsingin yliopistollinen sairaala, on tertiäärinen sairaala Suomessa. Sen osastoihin kuuluvat lastentaudit, kirurgiset osastot, syöpätaudit, elinsiirto-osasto ja vastasyntyneiden ja lasten teho-osastot. Sairaalassa on noin 130 vuodepaikkaa. Vuosittaisia hoitopäiviä tulee keskimäärin 30 000.

Kahdessa osatyössä oli mukana potilaita. Osatyössä 1., 149 veriviljelypositiivista infektiota sairastavan potilaan aineisto (iältään 0–17 vuotta) kerättiin vuosilta 2005–2012. Erityisasiantuntijat arvioivat kohdennetun mikrobilääkehoidon oikeellisuuden. Osatyössä 3. ei-rekisteröityjen mikrobilääkkeiden käytön prevalenssi tutkittiin kolmella erilaisella pediatriisella kohortilla. Suurin kohortti koostui ennenaikaisesti syntyneistä vastasyntyneiden teho-osaston potilaista (450–2000g), joilla oli veriviljelypositiivinen infektio ja infektiin annettu mikrobilääkehoito vuosina 2005–2014 (N=282). Kaiken kaikkiaan erilaisia metodeja käytettiin kvantitatiivisissa ja kvalitatiivisissa retrospektiivisissä potilastietojen analyysissä.

Osatyöt 2. ja 4. olivat rekisteritutkimuksia. Osatyössä 2. mikrobilääkkeiden kulutus vuosina 2003–2013 tutkittiin käyttäen DDD-lukuja. Osatyössä 4. analysoitiin raportoitujen mikrobilääkityspoikkeamien tyyppiä. Poikkeamat raportoituihin vapaaehtoisesti elektronisen HaiPro työkalun avulla terveydenhuollon ammattilaisten toimesta. Aineisto kerättiin vuosilta kesäkuu 2009 – joulukuu 2014. Suurin osa osatöistä tehtiin retrospektiivisesti. Analyysi oli sekä kvantitatiivista että kvalitatiivista.

TULOKSET

Mikrobilääkehoito oli epäasianmukaista 17% (26/149) potilaista, joilla oli veriviljelypositiivinen infektio (Osatyö 1.). Näistä potilaista kolme sai mikrobilääkehoitoa, joka oli täysin tehotonta taudinaiheuttajia vastaan *in vitro* aineiston mukaan. Suboptimaalista tai liian laajakirjoista mikrobilääkehoitoa annettiin 13/26 (50%) potilaista. Myös mikrobilääkehoitoon liittyvä kasvanut resistenssi havaittiin, tiettyjen anti-*Pseudomonas* mikrobilääkkeiden, kuten karbapeneemien, piperasilliini-tatsobaktaamin ja keftatsidiimin, käyttö kasvoi huomattavasti 11 vuoden aikana. (Osatyö 2.). Vuosina 2003–2013 resistenssi kasvoi useita beeta-laktaamiantibiootteja kohtaan. Merkittävin muutos oli karbapeneemien käytössä, joka kasvoi tutkimusaikavälillä 110%. Lastenlinikalla ei-rekisteröityjen lääkkeiden käyttö on suhteellisen yleistä. Vastasyntyneiden teho-osastolla 35% (7/20) käytetyistä mikrobilääkkeistä on ei-rekisteröityjä vastasyntyneillä vuosina 2009–2014 (Osatyö 3.). Kaiken kaikkiaan 18% (51/282) keskosista, joilla oli veriviljelypositiivinen infektio, sai ei-rekisteröityä mikrobilääkettä. Kasvun syntymäpainossa havaittiin olevan tilastollisesti merkittävästi yhteydessä ei-rekisteröityjen mikrobilääkkeiden käyttöön (odds ratio =0.85, 100g kasvua syntymäpainossa, p-arvo < 0.001). Lääkityspoikkeamat uhkasivat myös lastenlääkitysturvallisuutta. Osatyössä 4. raportoituihin 157 mikrobilääkityspoikkeamaa 149 potilaalla neljältä osastolta (GEN, NICU, HEM-ONC ja INF). Suurin osa raportoiduista poikkeamista (125/149, 84%) tapahtui potilaille. Kuolemaan johtavia poikkeamia ei sattunut. Kaksi raportoitua poikkeamaa oli kliinisesti merkittäviä (2/149, 1%). Suurin osa poikkeamista sattui mikrobilääkkeillä, joita käytettiin usein, kuten kefuroksiini (15/157, 10%) ja G penisilliini (15/157, 10%). Lääkkeen annon unohtaminen oli tyypillinen poikkeama mikrobilääkkeillä (37/149, 25%). Osatöiden 1.–4. tulokset varmistavat entisestään useita lastenlääkitysturvallisuutta heikentäviä tekijöitä sekä kasvaneen mikrobilääkeresistenssin sairaalassa.

JOHTOPÄÄTÖKSET

Nämä tutkimukset antoivat hyödyllisen yleiskuvan mikrobilääkehoidosta ja mikrobilääkkeiden käytöstä Lastenlinikalla. Asianmukaiseen mikrobilääkehoitoon ja lääkkeenmääääjien koulutukseen tulisi kiinnittää enemmän huomiota. Karbapeneemien kasvanut käyttö korostaa kasvanutta mikrobilääkeresistenssiä. Mitä pienempi syntymäpaino keskosella oli, sen todennäköisemmin keskonen sai ei-rekisteröityjä mikrobilääkkeitä. Mikrobilääkityspoikkeamat eivät onneksi olleet usein haitallisia potilaille. Tämä väitöstyö tarjoaa näkökulman tekijöihin, jotka heikentävät sairaalainfektioiden hoidon laatua lastensairaalassa, sekä edistää mikrobilääkkeiden käytön ohjausjärjestelmän rakentamista Lastenlinikalle.

Hakusanat: antibiootti, asianmukainen käyttö, bakteeri(t), bakteerilääke, bakteremia, ei-rekisteröityjen lääkkeiden käyttö, infektiaudit, lapset, lasten teho-osasto, lastensairaala, lääkekulutustiedot (DDD-luvut), lääkityspoikkeama, lääkitysturvallisuus, mikrobilääke, patogeeni, pediatriinen, mikrobilääkkeiden käytön ohjausjärjestelmä, rekisteröity käyttö, sepsis, sienilääke, vastasyntyneiden teho-osasto, vastasyntynyt, veriviljelypositiivinen infektio, viruslääke

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*”On yksi päivä jälleen mennyt muistoihin,
sen hetket eivät saavu takaisin.
On joka hetki vuorollansa arvokkain ja
tahdon kiittää kun sen elää sain.”*

*Tuomasyhteisö ry, Messulauluja kirja
(Laulu 112, Kiitos menneestä päivästä), 2006*

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred in the text by their Roman numerals.

- I Laine N., Vaara M., Anttila V.-J., Hoppu K., Laaksonen R., Airaksinen M., Saxen H. Evaluation of antimicrobial therapy of blood culture positive healthcare-associated infections in children, *PlosOne*, 2015
- II Laine N., Hoppu K., Airaksinen M., Saxen H. Antimicrobial consumption in a tertiary children's hospital in Finland (2003–2013), *European Journal of Hospital Pharmacy*, 2016
- III Laine N., Kaukonen A.-M., Hoppu K., Airaksinen M., Saxen H. Off-label use of antimicrobials in neonates in a tertiary children's hospital, *European Journal of Clinical Pharmacology*, 2017
- IV Laine N., Sunila L., Airaksinen M., Saxen H. Documented medication errors related to antimicrobial therapy in a tertiary children's hospital, Submitted to the *American Journal of Health-System Pharmacy*

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ABBREVIATIONS

ADME Absorption, Distribution, Metabolism and Excretion of drugs
AMT, antimicrobial therapy
ASP, antimicrobial stewardship program
ATC/DDD, Anatomical Therapeutic Chemical Classification System with
Defined Daily Doses defined by WHO
BSI, bloodstream infection
CDC, Centers for Disease Control and Prevention
CONS, coagulase-negative staphylococci
CRE, carbapenem-resistant *Enterobacteriaceae*
DDDs, Defined Daily Doses
ECDC, European Centre for Disease Prevention and Control
ESBL, extended-spectrum β -lactamase enzyme
GEN, Paediatric Kidney and Transplantation Ward
HCAI, healthcare-associated infection
HEM-ONC, Oncology and Transplantation Ward
HUCH, Helsinki University Central Hospital
HUS, Hospital District of Helsinki and Uusimaa
INF, Infectious Diseases and Observation Ward
LASA, look-alike and sound-alike medicines
MRSA, methicillin-resistant *Staphylococcus aureus*
MSSA, methicillin-sensitive *Staphylococcus aureus*
MSSE, methicillin-sensitive *Staphylococcus epidermidis*
NICU, Neonatal Intensive Care Unit
OR, odds ratio
PICU, Paediatric Intensive Care Unit
TDM, therapeutic drug monitoring
VRE, vancomycin-resistant *Enterococcus*

DEFINITIONS OF KEY CONCEPTS

Administration error, in Study IV administration errors include omission (forgetting to administer the drug), wrong dose/dosing interval, wrong drug given and otherwise inappropriate administration. This is due to the categorization in the HaiPro system.

GARPEC (Global Antimicrobial Resistance, Prescribing, and Efficacy among Neonates and Children). GARPEC project is a global surveillance network focused on collection of data on neonatal and paediatric antimicrobial prescribing and resistance.

Empirical antimicrobial therapy, antimicrobial given when infection is suspected and the causative pathogen is not yet known.

HaiPro, web-based tool for anonymous and voluntary reporting for healthcare professionals in Finland.

Healthcare-associated infection (HCAI), an infection that occurs in a patient during the process of care in a hospital or other healthcare facility that was not present or incubating at the time of admission.

Hospital-acquired bacteremia, in Study I, this was determined according to the classic CDC criteria, where laboratory-confirmed bloodstream infection is LCBI. LCBI is equivalent to the determination of healthcare-associated BSI in Study I.

Label drug, label use of a drug

Medication error, a medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

Neonate, child less than 30 days old

Off-label drug, in Study III off-label (OL) drug use was determined as following: Off-label drug use occurs when a drug is administered for indication(s) not given in drug's summary of product characteristics (SPC).

OL, off-label use of a drug

Omission error, forgetting to administer a drug on time

Premature neonate, in Study III premature neonates were neonates weighting 400–2000g

Sepsis, life-threatening organ dysfunction caused by a dysregulated host response to infection

Targeted antimicrobial therapy, antimicrobial therapy given after receiving final culture results on causative pathogens

1. INTRODUCTION

As users of pharmaceuticals, children are a vulnerable group, and more effort should be placed on research investigating appropriate use of drugs in paediatrics. There is a large gap in knowledge on how to safely and effectively use many different drugs in children. However, during the past decade, efforts have been conducted to increase the knowledge of drug use in children. One such effort is the Paediatric Regulation that came into force in 2007 [1]. Despite these recent positive developments in paediatric research, more knowledge is still required, particularly regarding data on dosing and pharmacokinetics [2]. Numerous issues, such as off-label use and extrapolating drug dosages from adult formulations to children, weaken paediatric medication safety. Dosages need to be adapted to paediatric patients based on age groups because the ADME processes (absorption, distribution, metabolism and excretion) vary according to age and the developmental processes of children.

Off-label (OL) use of drugs in children is common [3, 4]. It is estimated that out of all pharmaceuticals used in children, approximately 50% are being used OL. The use of OL drugs in children's hospitals varies between 12% and 71% [4, 5–12]. In certain groups of patients, such as neonates, it can be as high as between 48% and 89% [4, 5, 6, 10, 11]. In European NICUs (Neonatal Intensive Care Units), the prevalence of OL use was between 28% and 100% [13–17]. Furthermore, in premature neonates the prevalence of OL use is known to vary between 91% and 100% [13, 14, 16].

Despite common use of antimicrobials in hospitalized children, many antibiotics do not have a market authorization in paediatrics, especially in neonates (preterm and full-term) [2]. The OL use of antibiotics is relatively common in hospitalized children, although many antimicrobials lack data on dosing, pharmacokinetics, safety, efficacy and clinical use in paediatrics. This leads to a number of issues that threaten paediatric medication safety: lack of available dosage forms, individual doses must be calculated based on age, weight and/or body surface area, disease(s) and clinical condition. Adverse effects follow more often if drugs are used OL, and there is lack of research standards since no prescribing standard exists [18].

The use of drugs may also predispose patients to medication errors. The frequency of medication errors in children is more common than in adults [19]. In addition, when an error occurs, children are more prone to clinically significant harm [20]. Children are more prone to errors for numerous reasons [21], one being the relatively common use of OL drugs in children despite the fact that data on optimal doses, etc., are not available. It is estimated that medication errors are three times more likely to occur in children versus adults [22–33]. Medication errors occurring with

antimicrobial therapy (AMT) in children is an area lacking in research, with only a few studies focused on this area [28, 30]. Investigating the occurrence of medication errors is imperative in order to learn how to prevent these errors and to promote medication safety.

The judicious use of antimicrobials is of similarly high importance. Resistance towards antimicrobials is growing constantly [34]. In addition, the development of novel antimicrobials has not been very successful lately. It also requires time and major funding. Battling against antimicrobial resistance in hospital settings can be done in multiple ways, such as implementing antimicrobial stewardship programs (ASPs), monitoring the consumption of antimicrobials and focusing on the individual antimicrobial courses given to patients [35]. These measures should reduce the use of overly broad-spectrum antimicrobials and help reserve these precious drugs for circumstances where they are a necessity. The AMT should be carefully monitored during an infection. Starting an empirical AMT often involves the use of broad-spectrum antimicrobials when the causative pathogen(s) are unknown. However, after the microbiological results are available, especially results from the blood culture, the identification of the pathogen(s) allows us to re-evaluate the AMT. There are surprisingly few studies that have investigated the effect of blood culture results in the subsequent AMT in hospital infections in paediatrics. This would be important research since the use of overly broad-spectrum antimicrobials increases overall resistance and exposes patients to resistant microbes and adverse effects such as *C.Difficile* infections [36–38].

This dissertation investigates the use of antimicrobials in the Children's Hospital, Helsinki University Central Hospital. The aim of the dissertation was to improve the quality of AMT in the Children's Hospital as well as to produce data on the use of antimicrobials in children. The AMT given to children was investigated using different approaches that provided different data, which are presented in the following studies (I–IV). The appropriateness, quality and safety of AMT were investigated in individual patient cases as well as at the hospital level. The analysis was both qualitative and quantitative.

2. REVIEW OF THE LITERATURE

The literature reviews and literature searches were done regarding use of antimicrobials in children's hospitals. A literature review was conducted on the evaluation of appropriateness of antimicrobial therapy (AMT), and a systematic literature review was conducted on medication errors in hospitalized children. Off-label use of antimicrobials was investigated by comparing local and global categorizations and patterns of use.

2.1. HEALTHCARE-ASSOCIATED INFECTIONS IN CHILDREN

2.1.1. GENERAL PRINCIPLES OF HEALTHCARE-ASSOCIATED INFECTIONS

A healthcare-associated infection (HCAI) is an infection that occurs in a patient during the process of care in a hospital or other healthcare facility, which was not present or incubating at the time of admission [39]. When referring to HCAIs, the terms “hospital infection” and “nosocomial infection” are also used. HCAIs can start from an infected organ, such as bladder or lungs, and progress to bloodstream infection where the causative pathogen(s) are in the blood. Pathogens can also access the bloodstream directly from cannulas or via other invasive routes, for example, during surgery. Incubation time varies according to causative pathogen(s), and infections emerging when the patient is hospitalized should be considered as HCAIs. When the causative agent is bacteria, HCAI usually becomes detectable in 48 hours [40].

The burden resulting from HCAIs is enormous. Worldwide, HCAIs affect the lives of hundreds of million patients annually [39]. HCAIs are associated with prolonged hospital stays, disability, antimicrobial resistance, rising costs for healthcare systems and an increased burden on patients and their families. In addition, significant mortality and morbidity can be caused by HCAIs, and this is especially true in neonates with central line -associated bloodstream infections and ventilator-associated pneumonia [41–44].

2.1.2. HEALTHCARE-ASSOCIATED INFECTIONS IN PAEDIATRICS

The most common bacterial HCAIs in children are surgical site infections (SSIs), lower respiratory tract infections and bloodstream infections (BSIs) [45]. The prevalence of HCAIs in European paediatric hospitals varies between 1.2% and

10.4% [46]. There is also variation between different medical wards regarding the prevalence of HCAs. The highest rates have been recorded in paediatric intensive care units and neonatal intensive care units (PICUs and NICUs) [46, 47]. In the Children's Hospital, healthcare-associated infections have most often been reported in patients on haematology and neonatology wards [48]. The prevalence of HCAs in children has been published to be the highest during the first year of life [46]. Overall, the prevalence of HCAs has been reported to be between 9% and 21% in critically ill children [41, 49–51].

The causative pathogens in paediatric HCAs are mostly bacteria. According to a study from the European Centre for Disease Prevention and Control (ECDC) conducted in European children's hospitals, 88% of causative pathogens in HCAs were bacteria, 7% fungi and 5% viruses [46]. The most common bacteria identified were coagulase-negative staphylococci (CONS), *Enterobacteriaceae* and *Staphylococcus aureus*. Respiratory infections caused by viruses are also very frequent pathogens. Rotavirus and norovirus are common causative pathogens in gastroenteritis. However, infections caused by fungi, such as *Candida*, are relatively rare.

2.1.3. BLOODSTREAM INFECTIONS IN PAEDIATRICS

Bloodstream infections (BSIs) are infections where the pathogens, usually bacteria, can be identified from a blood culture sample. Blood culture positive infections are infections where the pathogen has been identified from the blood culture sample. Very frequently the blood culture remains negative. This does not, however, mean that the infections are not caused by bacteria. A negative culture may reflect low numbers of bacteria in the blood. Such infections are called culture negative infections. They may also be referred to as clinical infections with negative blood cultures. BSIs are among the most common HCAs in paediatrics [52–54]. In European paediatric hospitals, BSIs were the most common HCAs representing 41.0–48.1% of all HCAs recorded [46]. The majority of the BSIs were reported in infants less than 12 months of age. In the Children's Hospital, the prevalence of blood culture positive infections has been reported to be 1.6 infections/1000 days of care (Figure 1).

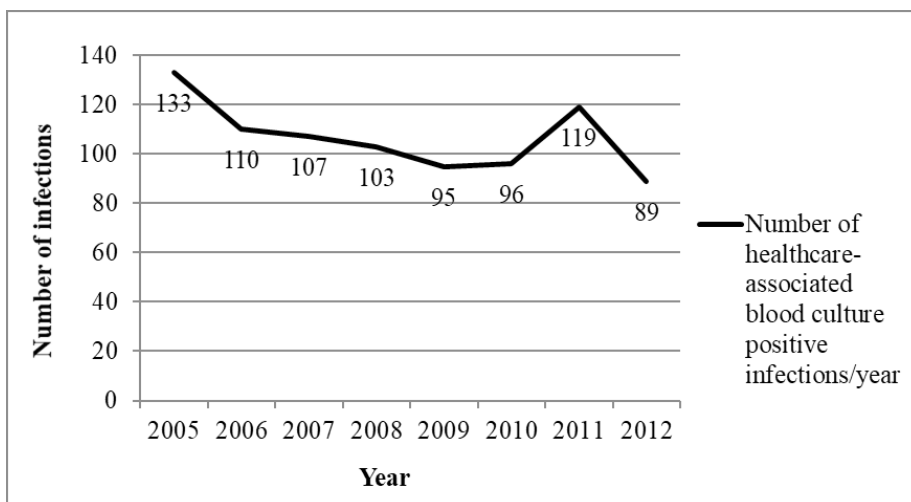


Figure 1. Number of healthcare-associated blood culture positive infections/year in the Children's Hospital, Helsinki University Hospital from 2005–2012.

The most common causative pathogens of blood culture positive infections were Gram positive cocci in the Children's Hospital (Figure 2). Bacteremias can progress to sepsis, which is a life-threatening organ dysfunction caused by a dysregulated host response to infection [55]. Furthermore, in septic shock, circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Recently, a new score to describe sepsis was developed [56]. The Sepsis-related Organ Failure Assessment (SOFA) score is more accurate than the numerous previous definitions, and it can be used both to monitor the patient and to calculate the patient's prognosis.

When a BSI is suspected, rapid initiation of adequate empirical antimicrobial therapy (AMT) is of paramount importance. The selection of appropriate therapy is, however, challenging since it should cover the most likely causative pathogens. It has been shown by Welsh *et al.* [57] that selection of suboptimal therapy clearly affects the prognosis of the patient. On the other hand, the use of an excessively broad-spectrum antimicrobial therapy can expose the patient to opportunistic infections caused by multiresistant organisms, fungi or *Clostridium difficile* colitis. In addition, multiple co-morbidities in the patient as well as numerous side effects of the antibiotics further complicate the choice of appropriate therapies.

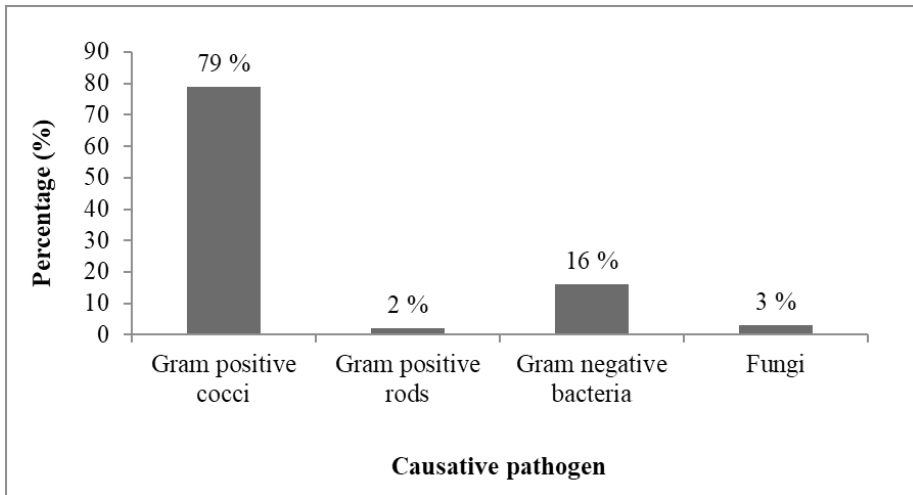


Figure 2. 944 episodes of blood culture positive infections in 793 children in the Children's Hospital, Helsinki University Hospital from 2005-2012.

2.2. ANTIMICROBIAL THERAPY FOR HEALTHCARE-ASSOCIATED INFECTIONS

2.2.1. EMPIRICAL AND TARGETED ANTIMICROBIAL THERAPY

When an infection is suspected in a hospitalized patient, initiating AMT as soon as possible is of crucial importance. AMT is empirical until the pathogens are identified from samples such as urine, sputum or blood culture. Hence, empirical AMT is aimed at the most probable causative pathogens and is generally of broader spectrum compared to targeted AMT. When prescribing targeted AMT, the causative pathogens are known and AMT can be more focused (de-escalated) towards the identified pathogens.

2.2.2. APPROPRIATENESS AND INAPPROPRIATENESS OF ANTIMICROBIAL THERAPY FOR HEALTHCARE-ASSOCIATED INFECTIONS

Inappropriate use of AMT occurs in several ways, such as prescribing antibiotics with no or suboptimal efficacy against the pathogens. In addition, failure of de-escalation of the therapy should also be considered inappropriate. Investigating the quality of AMT is a complex topic requiring multiple factors to be considered. Hence, a MedLine-based literature review was conducted in January 2012 in order

to discover how appropriate or inappropriate AMT for HCAIs had been used in different hospital settings (Table 1.). Studies conducted in adults were included since no studies focusing on paediatrics were found.

Table 1. Inclusion criteria for the literature review appropriate vs. inappropriate antimicrobial therapy (AMT) for HCAIs (healthcare-associated infections).

- study conducted from the year 2000 onwards
- language English
- study conducted in hospital environment
- both paediatric and adult studies were included
- study on AMT in hospitalized patients
- search terms: bloodstream infection, blood culture positive infection, sepsis, hospital, antimicrobial therapy, antibiotic, inappropriate, appropriate, paediatric

The search yielded 392 articles, of which 10 met the inclusion criteria (Tables 1. and 2.). The majority of the studies focused on adults. These studies applied different approaches and used a large variety of definitions of appropriate AMT (Table 3.). Some studies evaluated only the appropriateness of empiric therapy of serious infections [58–60], while others looked at targeted therapy as well [60–65]. Some of the studies focused specifically on verified BSI [58–60, 65] and others on the quality of the AMT in general [62,73].

Three studies focused on appropriateness of empirical AMT. These three studies had similar, relatively simple definitions of appropriate empirical AMT [58–60]. Two studies, Erbay *et al.* and Harbarth *et al.*, defined the window of time when the appropriateness should be evaluated. In the study by Erbay *et al.*, empirical AMT was appropriate if at least one antibiotic was active towards the causative pathogen(s) within 48 hours after acquisition of the blood culture results [58]. Harbarth *et al.* concluded that AMT was inappropriate if a patient did not receive at least one antimicrobial agent to which the causative microorganisms were susceptible within 24 hours of the diagnosis of severe sepsis [59]. Zaragoza *et al.* considered empirical AMT to be inappropriate if infection was not being effectively treated at the time the causative microorganism and its antibiotic susceptibility were known [60].

Six of the studies used relatively simple definitions of inappropriate AMT, whether empirical or targeted or both (Table 3.) [58–60, 62, 64–65]. For example, a study by Davey *et al.* defined AMT as inappropriate if the pathogen was resistant to the antimicrobial agent used or initiation of the appropriate AMT was delayed [62]. This study concluded that if a patient received appropriate empirical AMT and the therapy was thereafter promptly targeted, the outcome was better than if the empirical AMT

had been inappropriate but had been switched to appropriate targeted therapy. A study by Raineri *et al.* defined appropriateness versus inappropriateness in the following way: AMT was appropriate when the prescribed drug was shown to be active (*in vitro*) against the pathogens and was administered at adequate doses + time intervals, and AMT was inappropriate when the infection was not treated due to incorrect antimicrobial choice, presence of resistant pathogens, incorrect dosage, incorrect duration or the mycotic infection was not treated [64]. Moreover, Suppli *et al.* defined the appropriate AMT for BSIs to be any therapy with documented clinical effect, *in vitro* activity and a minimum treatment length of 6 days [65]. Other studies used more complex and detailed definitions for the appropriateness of AMT [61, 63, 66]. Willemsen *et al.* used a score system to evaluate the appropriateness of the AMT [66]. The score system divided the therapies into five different categories: correct decision, incorrect decision, incorrect choice, incorrect use and data missing. They further speculated that when evaluating incorrect use, the following parameters should also be taken into account: dosage, timing, administration and duration of therapy.

Table 2. Comparison of articles (N=10) accepted to literature review describing appropriate and/or inappropriate antimicrobial therapy in general in hospitalized patients or hospitalized patients with bloodstream infections (BSIs), sepsis or other HCAs (healthcare-associated infections).

| Author and year | Article | Research type | Patient group included | Only appropriateness of empirical AMT covered | Precise classification for AMT | Classification for appropriateness of AMT not clear | Both classification system of inappropriate and appropriate AMT are covered |
|-----------------------------|--|---------------|---|---|--------------------------------|---|---|
| Borer <i>et al.</i> 2001 | A proposed tool for standardized assessment of appropriateness of antibiotic therapy | T | No patients included, the study introduced a tool for the assessment of AMT | no | yes | no | yes |
| Cosgrove <i>et al.</i> 2007 | Impact of different methods of feedback to clinicians after postprescription antimicrobial review based on the Centers for Disease Control and Prevention's 12 steps to prevent antimicrobial resistance among hospitalized adults | R | Hospitalized adults with different infections | no | yes | no | yes |
| Davey <i>et al.</i> 2008 | Appropriate vs. inappropriate antimicrobial therapy | RE | Several studies, different patient populations | no | no | yes | yes |
| Erbay <i>et al.</i> 2009 | Impact of early appropriate antimicrobial therapy on survival in <i>Acinetobacter baumannii</i> bloodstream infections | R | <i>Acinetobacter baumannii</i> bloodstream infections in adults | yes | no | no | no |

| | | | | | | | |
|---|---|---|--|-----|-----|-----|-----|
| Harbarth <i>et al.</i> 2003 | Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. | R | Adult patients with sepsis | yes | no | yes | no |
| Kumar <i>et al.</i> 2009 | Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock | R | Adult patients with sepsis | no | yes | no | yes |
| Raineri <i>et al.</i> 2008 | Role of the infectious diseases specialist on the appropriateness of antimicrobial therapy prescription in an intensive care unit | R | ICU patients | no | yes | no | yes |
| Suppli <i>et al.</i> 2011 | Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy | R | <i>Enterococcal</i> bloodstream infections in adults | no | yes | no | no |
| Willemsen <i>et al.</i> 2007 | Appropriateness of antimicrobial therapy measured by repeated prevalence surveys | S | Hospitalized adults with different infections | no | yes | no | yes |
| Zaragoza <i>et al.</i> 2003 | The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in intensive care unit | R | Adult patients with sepsis | yes | no | yes | no |

AMT=antimicrobial therapy, ICU=intensive care unit, R=retrospective research, RE=literature review, S=survey study, T=study developing a tool.

Table 3. Different appropriate vs. inappropriate definitions for antimicrobial therapy (AMT).

| Study | Definition of appropriate vs. inappropriate AMT |
|--|--|
| Borer <i>et al.</i> 2001 | <p>A proposed tool for standardized assessment of appropriateness of antibiotic therapy</p> <ol style="list-style-type: none"> 1. All components of therapy were agreeable. 2. Agreement with used drug, but one of the following is inappropriate: <ol style="list-style-type: none"> a) Dose/dosing interval, b) Duration of therapy: too short or long c) Timing of initiation: too soon, too late 3. Antibiotics are indicated, but other agents should be used due to: <ol style="list-style-type: none"> a) Disease severity/underlying disease b) Resolution of attempted diagnosis (symptomatic, anatomic, etiologic) c) Safety profile d) Cost of therapy e) Known drug allergy f) Dual therapy indicated g) According to Stanford guide. 4. Disagreement with the need of antibiotics. |
| Cosgrove <i>et al.</i> 2007 | <p>Impact of different methods of feedback to clinicians after postprescription antimicrobial review based on the Centers for Disease Control and Prevention's 12 steps to prevent antimicrobial resistance among hospitalized adults</p> <p>A course of therapy was defined as suboptimal if any of the following criteria were met:</p> <ol style="list-style-type: none"> 1. Empirical therapy was no longer indicated because of lack of evidence of an infectious process requiring antibiotics, on the basis of microbiologic and radiologic findings and the presence of an alternative diagnosis 2. The organisms isolated were not susceptible to the agent prescribed or were susceptible to a narrower-spectrum agent 3. Vancomycin use was unnecessary, on the basis of Healthcare Infection Control Practices Advisory Committee guidelines 4. Antimicrobial coverage was excessive or overlapping (excluding combination therapy for infections caused by organisms with inducible β-lactamase production: <i>Serratia</i> species, <i>Pseudomonas aeruginosa</i>, <i>Acinetobacter</i> species, <i>Citrobacter</i> species, and <i>Enterobacter</i> species) 5. Surgical prophylaxis was continued for more than 24 hours after the procedure 6. The empirical therapy chosen was incorrect; and/or 7. Oral therapy would be acceptable to treat the infection. |
| Davey <i>et al.</i> 2008 | <p>Appropriate vs. inappropriate antimicrobial therapy</p> <p>Inappropriate antimicrobial treatment is defined as: use of antimicrobial agent to which a pathogen is resistant or a delay in starting appropriate treatment</p> |

| | | |
|---------------------------------------|--|---|
| <p>Kumar et al. 2009</p> | <p>Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock</p> | <p>1. The following were considered appropriate therapy even in the absence of specific sensitivity testing: (a) Group A, B and G Streptococcus treated with all β-lactams; (b) All Gram positive bacteria except enterococci treated with vancomycin; (c) Anaerobes treated with metronidazole, beta-lactam inhibitor combinations, and carbapenems; and (d) Organisms treated with beta-lactamase inhibitor combinations if treated with the beta-lactam alone.</p> <p>2. The following were considered inappropriate therapy even in absence of specific sensitivity testing: (a) Enterococci treated with all cephalosporins and trimethoprim/sulfamethoxazole; (b) <i>Enterococcus faecalis</i> sensitive to quinupristin-dalfopristin; and (c) Any bacteria treated with monotherapy with aminoglycoside at standard dosing every 8 h.</p> <p>3. Legionella species were considered appropriately treated with macrolides or quinolones.</p> <p>4. Treatment with oral or IV metronidazole or oral vancomycin along with broad-spectrum antienteric antimicrobial therapy was considered to be a requirement for appropriate antimicrobial therapy of septic shock caused by <i>Clostridium difficile</i> enterocolitis.</p> <p>5. Clindamycin, macrolides and third-generation cephalosporins were not considered appropriate for the treatment of <i>S aureus</i> infection irrespective of listed sensitivity.</p> <p>6. Cefotaxime and ceftriaxone were not considered appropriate therapy for <i>Pseudomonas aeruginosa</i> infection irrespective of listed sensitivity.</p> <p>7. In cases where multiple isolates were found at a local site, appropriate therapy was considered to have been delivered if the densest pathogen was covered. If multiple pathogens were isolated at a similar density, all pathogens were required to have been covered.</p> <p>8. For multiple simultaneous blood isolates, appropriate therapy had to cover all pathogens.</p> |
| <p>Raineri et al. 2008</p> | <p>Role of the infectious diseases specialist in the appropriateness of antimicrobial therapy prescription in an intensive care unit</p> | <p>Appropriate when: prescribed drug shown to be active (in vitro) against the pathogens and was administered at adequate doses + time intervals. Inappropriate when: infection not treated, not correct, antimicrobial choice, presence of resistant pathogens, incorrect dosage, incorrect duration, mycotic infection not treated.</p> |

| | | |
|--|---|--|
| Suppli <i>et al.</i> 2011 | Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy | Appropriate AMT was defined as: any therapy with documented clinical effect + in vitro activity + a minimum treatment length of 6 days. |
| Willmsen <i>et al.</i> 2007 | Appropriateness of antimicrobial therapy measured by repeated prevalence surveys | 1. Correct decision (appropriate use) 1.1 No AMT and no infection and no AMT needed 1.2 No AMT and infection and no AMT needed 1.3 AMT and infection and appropriate choice and appropriate use. 2. Incorrect decision (inappropriate use) 2.1 No AMT and infection and AMT needed 2.2 AMT and no infection and no prophylaxis and no AMT needed 2.3 AMT and no infection and prophylaxis and no AMT needed. 3. Incorrect choice (inappropriate use) 3.1 Divergence from guidelines. 4. Missing data (insufficient information) 4.1 No AMT and not enough diagnostic information about infection 4.2 Infection and not enough diagnostic information if AMT is needed 4.3 AMT and not enough diagnostic information about infection 4.4 Infection and not enough information about AMT. |

Regarding the choice of antimicrobial, excessive use of vancomycin has been reported by several studies. The study by Cosgrove *et al.* investigated prospectively clinicians' antimicrobial prescriptions for different empirical healthcare infections [61]. AMT was criticized in 30% (334/1104) of the cases. In 60/334 (18%) cases, unnecessary use of vancomycin was recorded. Patel *et al.* investigated the use of AMT in neonatal infections and likewise recorded frequently inappropriate vancomycin use [67]. Vancomycin can be inappropriately used in multiple ways. Common ways include prescribing vancomycin unnecessarily for empiric AMT and targeted AMT even though there are narrower spectrum and effective antimicrobial(s) available [68–71]. The reason for excessive use of vancomycin is not clear. One reason may be that many guidelines for empiric therapy include vancomycin, but once the data on the pathogen have been exposed, de-escalation is not executed. Increased provider awareness of drug-resistant CONS probably also increases the overall use of vancomycin. Similar findings have been published by Levy *et al.* [72].

Two studies compared the antimicrobial therapy used to local protocols or national guidelines [64, 66], and a study by Borer *et al.* proposed a standardized tool for the assessment of appropriateness of AMT [73]. In a study by Raineri *et al.*, a systematic infectious diseases specialist consultation program was implemented in the ICU setting. After implementation, adherence to local guidelines regarding empirical AMT was increased by more than 20% (63% vs. 84%) [64]. Willemsen *et al.* investigated the appropriateness of AMT and found that during six prevalence studies conducted from 2001 to 2004, the appropriateness of AMT did not vary a great deal. The appropriateness of AMT was evaluated against the local AMT prescription guidelines. Out of 938 patients with AMT, 351 (37%) received inappropriate AMT.

Overall, the proportion of patients receiving inappropriate AMT varied between studies. The percentage of patients receiving inappropriate AMT varied (20–24%) in empirical AMT [59, 60, 63] and in targeted AMT (16–37%) [63–65].

There are a few methodological considerations regarding the literature review on appropriate AMT for BSIs or appropriateness of AMT in general. The studies included in the review were of adult patients or did not include patients and discussing appropriateness of AMT only on a general level (Tables 2. and 3.). Research conducted in paediatrics on this area is scarce. Likewise, the number of patients in the studies included was relative low, which does not necessarily provide enough evidence on what type of evaluation is effective when assessing AMT for BSIs or in general. Another concern was that few studies focussed on assessing AMT from a narrow point of view, such as covering only one or a few different types of pathogens and used AMT for those circumstances. The evaluation of appropriateness of AMT in individual patients depends on the pathogens identified, local resistance pattern, infection sources, co-morbidities and whether the patient is a child or adult.

2.2.3. OUTCOME OF ANTIMICROBIAL THERAPY FOR BLOODSTREAM INFECTIONS

Due to the small number of studies investigating the appropriateness of AMT, it is unclear how often inappropriate AMT has been used in the treatment of patients with healthcare-associated BSIs. Appropriate empirical AMT for BSI is known to reduce the mortality in sepsis [59] and in enterococcal infections [65]. In addition, Erbay *et al.* showed that in bacteremias caused by *Acinetobacter baumannii* infections, a 26% reduction in the overall mortality rate was achieved with adequate early empirical antimicrobial therapy compared with inadequate therapy [58]. Similarly, Kumar *et al.* showed that inappropriate empirical AMT in septic shock was associated with a fivefold increase in mortality [63]. In addition, Raineri *et al.* demonstrated in patients with different types of serious infections that appropriate AMT was associated with decreased mortality [64]. In contrast to these studies, Zaragoza *et al.* showed that inappropriate AMT was not associated with increased mortality [60]. This uncommon result was perhaps related to the causative organism(s) or origin of the bacteremia.

2.3. ANTIMICROBIAL THERAPY FOR HOSPITALIZED CHILDREN

2.3.1. OFF-LABEL USE OF ANTIMICROBIALS

For market authorization labelling, data on the safety and efficacy of pharmaceuticals must be submitted to the regulatory authorities by the pharmaceutical companies. Based on the data submitted, a drug can be authorized by the regulatory authorities, and the approved labelling, with information on indication and dosing and in the age groups the drug has been approved for, is available in the Summary of Product Characteristics (SmPC). A drug is used off-label (OL) if it is used in a manner not recommended in the SmPC. OL use can be related to age, indication, contraindication, dose, age-appropriate formulation and route of administration. Dose and formulation (route of administration and *ex tempore* preparations) are the most common OL use categories in children [3, 5–8]. The fact that a drug is used OL does not necessarily mean that there is no evidence of its safety and efficacy [74].

The OL use of drugs in children is common [3, 4]. It is estimated that out of all pharmaceuticals used in children, approximately 50% are being used OL. The frequency of OL use depends on many factors, including point of care (community vs. hospital), co-morbidities and age. The use of OL drugs in children's hospitals varies between 12% and 71% [4, 5–12]. In certain groups of patients, such as neonates, it can be as high as between 48% and 89% [4–6, 10–11]. In European NICUs (Neonatal Intensive Care Units), the prevalence of OL use was between 28% and 100% [13–16]. Furthermore, in premature neonates the prevalence of OL use is known to vary between 91% and 100% [13, 14, 16].

The safety and efficacy of novel antimicrobials (antibacterials, antifungals and antivirals) have only seldom been tested in neonates. However, some progress has been made after the introduction of the Paediatric Regulation in 2007 [17]. The number of clinical trials among neonates has slowly increased. Despite the OL use of antimicrobials being relatively uncommon compared to other groups of pharmaceuticals, the situation is far from satisfactory [75]. To obtain data on the frequency of OL use of antimicrobials in neonates, this use was investigated among hospitalized patients.

As the examples discussed above indicate, OL status does not necessarily mean that the drug is not safe and effective to use in neonates or children. Research data related to dose, efficacy and safety may be available but have not been submitted to regulatory authorities for labelling. Age-appropriate dosing recommendations for children may be found for some commonly used drugs not labelled for children in formularies like BNFC (British National Formulary for Children) and databases such as Micromedex^R (US). These recommendations are given by clinical professionals, and the recommendations are based on academic research and clinical experience. However, there are often no clear and exact recommendations for the youngest age group, i.e., the premature neonates. Many antimicrobials used OL have established their place in the management of infectious diseases in neonates. Despite recent positive development in paediatric research, efforts are still needed, particularly regarding data on dosing and pharmacokinetics [75].

2.3.2. DOSING AND FORMULATIONS OF ANTIMICROBIALS

The optimal dosing of many antimicrobials for paediatric patients is not known [3, 5–8]. In the Children's Hospital, the most common antimicrobials for BSIs used OL (according to Finnish National Drug Formulary, Pharmaca Fennica®) are listed in Table 4. Some antimicrobials, despite being on the market for decades, still lack official market authorization. As can be seen from Table 4., many commonly used antimicrobials do not have dosing recommendations for children. This is especially true with neonates.

Due to relatively common OL use of antimicrobials in paediatrics, there are not always ready formulations that can be used. Hence, nurses and pharmacists prepare formulations suitable for children (ex temporaneous preparations) from the formulations aimed at adult use. This exposes children to compromised quality of care and medication errors. For example, the amount of dilution added to the adult product may not have been calculated correctly. Diluting antimicrobials is sometimes necessary in order to administer the drugs intravenously or via other routes to a child. A child receiving inappropriately prepared drugs may experience overdose or inefficient therapy due to concentrations of the drug that are too low.

Table 4. Commonly used off-label (OL) antimicrobials in neonates in the Children's Hospital combined with historical timeline including year of market authorization and Finnish national formulary recommendations compared to two databases: BNFC, British National Formulary for Children (UK) and Micromedex (US). N =no recommendations given (OL use) Y =recommendations given

| Antimicrobial | Year of market authorization in Finland | Recommended dosing given / or otherwise recommended for use in 0–30 days old neonates N =no recommendations given Y =recommendations given = | | |
|----------------|---|---|--|---|
| | | Finnish national formulary (Pharmaca Fennica), book 2015 and age of a child with which drug considered OL use | BNFC, British National Formulary for Children, book 2014–2015 and age of a child with which drug considered OL use | Micromedex (Truven Health Analytics), used via Internet in December 2015 and age of a child with which drug considered OL use |
| Amphotericin | 1966 | N < 1 month | Y | Y |
| Trimethoprim | 1972 | N < 3 months | Y | N Tablets < 12 years |
| Clindamycin | 1974 (po and iv) | N < 1 month (po, iv). | Y | Y Septicemia |
| Doxicycline | 1974 (iv), 1993 (po) | N < 8 years | N < 12 years | N < 8 years |
| Rifampicin | 1976 | N < 3 month | Y | Y |
| Ciprofloxacin | 1989 (po), 2007 (iv) | N < 12 years | N < 1 year | Y* (<1500g neonates) |
| Azithromycin | 1994 | N < 1 year | N < 6 months | Y Recommendations given < 6 months |
| Clarithromycin | 1994 (po), 2011 (iv) | N < 6 months old (po) and < 18 year olds (iv). | N < 1 month | N < 1 month old |

| | | | | |
|------------------------------------|-------------------------|--|------------------------------|--|
| Piperacillin tazobactam | 1994 | N < 2 years | N < 1 month | N < 12 years |
| Meropenem | 1995 | N < 3 months | Y | Y* (gestational age < 32 weeks and postnatal age < 2 weeks) |
| Levofloxacin | 1997 (po and iv) | N "Not for children." | N Age not clearly mentioned. | N < 6 months |
| Caspofungin | 2001 | N < 1 years | N < 2 years | N < 3 months |
| Linezolid | 2001 | N < 18 years | Y | Y* (<34 weeks neonates), VRE infections ∞ |
| Valganciclovir | 2002 | N "Safety and efficacy has not been assured in children." | Not mentioned. | Y |
| Posaconazole | 2005 (po), 2014 (iv) | N < 18 years | Not mentioned. | N < 13 years |

* Premature neonates mentioned. ∞ VRE, vancomycin resistant enterococci.

2.3.3. ANTIMICROBIAL MEDICATION ERRORS IN CHILDREN

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient [76]. The frequency of medication errors in children is more common than in adults [19]. Moreover, when errors occur, children are more prone to clinically significant harm [20]. Compared to adults, children are prone to errors for numerous reasons [21]. Many drugs lack data on dosing, pharmacokinetics, safety, efficacy and clinical use in paediatrics. In addition, many drugs are not authorized for use in paediatrics. This leads to a number of issues that compromise paediatric medication safety: lack of available dosage forms, individual doses must be calculated based on age, weight and/or body surface area, disease(s) and clinical condition. There are few published articles focusing on medication errors in paediatrics. Hence, a systematic literature review was conducted between January 18th and 20th, 2016, regarding medication errors in hospitalized paediatric patients. The search strategy was not aimed solely at antimicrobial medication errors but covered all types of medication errors in paediatric patients. Altogether, 333 articles were found of which 12 were eligible for review according to exclusion and inclusion criteria (Tables 5., 6. and 7. and Figure 3.).

According to the literature review, it has been estimated that medication errors are three times more likely to occur in children versus adults [22–33]. Studies included in the systematic literature review focused on the different points of process where the medication errors occur in paediatrics. The different points were presented as follows: prescription errors (5/12 studies), preparation of drugs (1/12 studies), administration of drugs (4/12 studies) and all types of medication errors (6/12 studies) (Table 7.).

Table 5. Search strategy regarding systematic literature review on medication errors in paediatrics in hospital.

| Article sources: Cinahl, Cochrane Library, Medic, Medline (Ovid), Pubmed, Scopus | | | | | |
|--|---|----------|---|------------------------------------|--|
| Search terms | Child* OR Pediatric* OR Paediatric | AND | Medication error | AND | Hospital |
| Additional search terms | Error report* OR Medication error OR Incident report* | AND/OR | Patient safe* Medication safe* (safety) | AND/OR | High risk medication or high alert medication |
| Additional inclusion criteria | English language | Human(s) | | Published between 2000 and 2016 | |

Table 6. Exclusion criteria and inclusion criteria for articles accepted for systematic review regarding medication errors in paediatrics.

| | Inclusion criteria | Exclusion criteria |
|--|--|--|
| Focus of research | Children, hospital or medical ward, pharmacotherapy | Adults, home or daycare, food, nutrition |
| Type of publication | Original research where aim(s), methods, results and analysis are described | Recommendations not based on research, literature reviews, reports, expert opinions |
| Medication error | Medication error that either reached the patient or was a near miss | Article was solely focused on adverse effects |
| Prevention of medication errors | New method has been invented and the functionality of the method is being tested | Other safety issues besides medicine-related are investigated, such as patient safety overall or safety of equipment |
| Availability | Article was fully available without any costs via University of Helsinki's library or via Internet (open access) | Article not available without costs via University of Helsinki library |

Patients included in the studies were from different kinds of wards in 5/12 studies, in ICU/PICU/NICU in 4/12 studies, in GEN in 3/12 studies, were oncology patients in 2/12 studies and were patients of SURG in one study (Table 7).

The prevalence of reported medication errors in children's hospitals varied between 13–19% [25, 26, 28, 30]. Administration errors were commonly identified with an 18–19% occurrence [21, 24]. Prevalence of omission errors were likewise relatively common ranging between 12–23% [23, 26, 33]. Doses that were too high were identified by many studies, with prevalence ranging from 12–24% [24, 33, 40]. Look-alike and sound-alike (LASA) medicines were involved in 36% of cases of incorrect medication [30]. The causes of medication errors were reported as the following: communication (20–34%) and lack of following policy or procedures (22–41%) [30, 33]. In addition, nurses reported excessive work load and distractions that undermine the quality of care [29]. Several studies reported that despite the relatively high occurrence of medication errors, none of them were identified as leading to permanent injury or severe clinical harm [24, 25, 30]. One study did, however, report an incidence rate of 0.1% in errors causing severe harm [31].

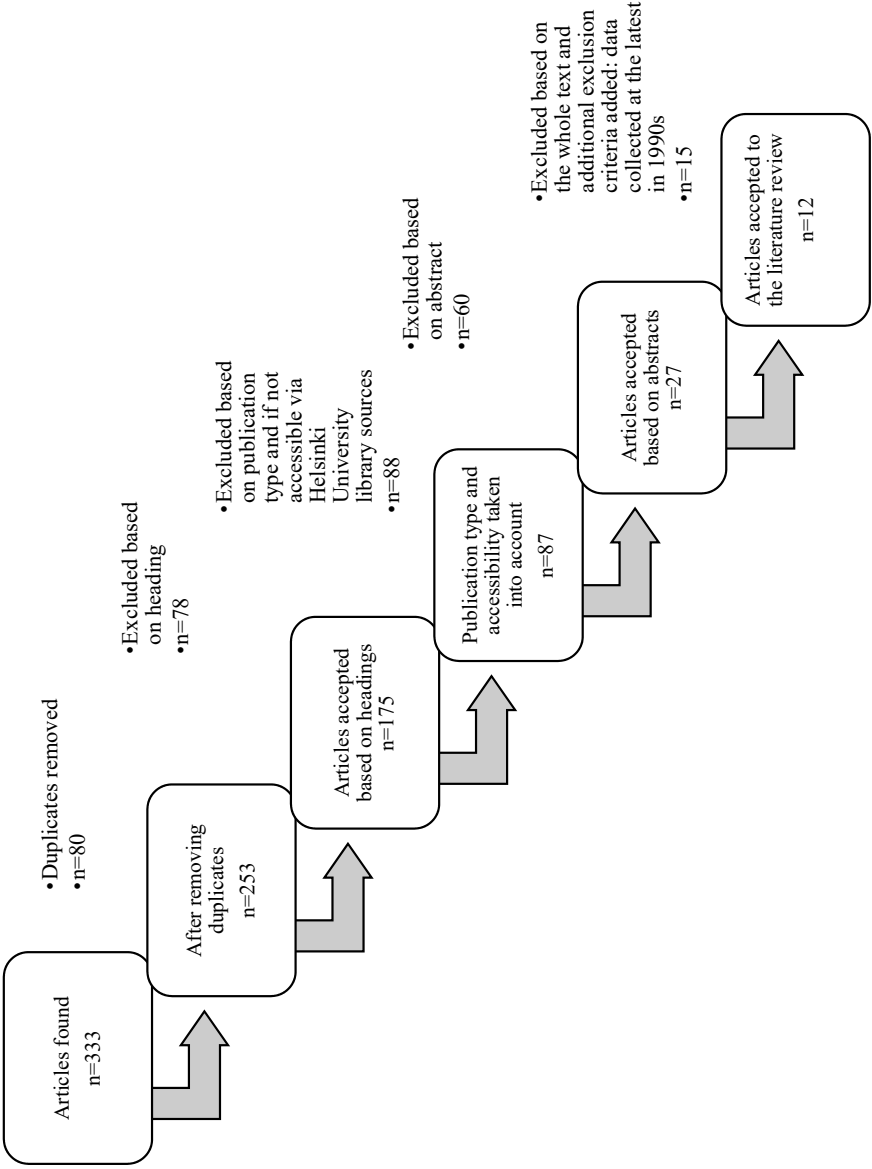


Figure 3. Flow selection of articles to systematic literature review covering medication errors in hospitalized children.

Table 7. 12 articles included to systematic literature review regarding paediatric medication errors at hospitals.

| Author(s), year and country | Aim(s) | Methods | Data | Medication error types included | Results | Conclusions |
|-------------------------------------|---|---------|--|---------------------------------|---|---|
| Alsulami et al. 2014 UK | To investigate how well nurses adhere to double-checking protocol in paediatric medical wards and to investigate what kind of medication errors occur in administration errors. | P, O | GEN, SURG, PICU, NICU wards 2012 | -preparation -administration | 2000 cases of administering/preparing drugs were evaluated. Medication administration errors (n = 191) or deviations from policy were observed, at a rate of 9.6% of drug administrations. Independent drug dose calculation, rate of administering intravenous bolus drugs and labelling of flush syringes were the steps with lowest adherence rates. | There was variation between paediatric nurses' adherence to double-checking steps during medication administration. The most frequent type of administration errors or deviation from policy involved the medicine being given to the parents to administer to the child when the nurse was not present. |
| Belela et al. 2011 Brasil | To describe medication errors in oncology patients treated in ICU. | E, D | ONC patients in ICU | -all types of errors | 110 medication errors reported on 71 forms. The omission error was the most common error type reported (22.7%), followed by administration error (18.2%). No harm to patients was reported in 83.1% of the notifications. Special focus should be cytotoxic medicines and antibiotics. | The analysis of the 110 medication errors provides evidence of the context of their occurrence and the need to implement measures that can prevent or intercept these errors. In an institution without adverse events report and a formal system too patient safety analysis, the implementation of a local non-punitive approach to medication errors notification represented an important tool to patient safety promotion. |
| Chua et al. 2010 Malaysia | To investigate the types and numbers of administration errors in two paediatric wards and to discover ways to avoid these errors. | O | GEN, ONC wards 10 days observation period | -administration -preparation | 857 drug administrations observed, error rate, 11.7%. The most common types of drug administration errors were incorrect time of administration (28.8%), followed by incorrect drug preparation (26%), omission errors (16.3%) and incorrect dose (11.5%). No error was life-threatening, 40% might have caused harm for the patient. | Drug administration errors are as common in paediatric wards in Malaysia as in other countries. Double-checking should be conducted, as this could reduce drug administration errors by about 20%, but collaborative efforts between all healthcare professionals are essential. |

2. Review of the literature

| | | | | | | |
|--|--|-------|---|----------------------------------|---|---|
| Dhjamina <i>et al.</i> 2014 India | To observe i.v. administered oncology medicines in order to build protective measures to minimize errors. | O | ONC 2012 | -prescription -administration | 23 errors were discovered (23/205, 11%), from those 6 were identified due to double checking procedure and error reaching the patient occurred in 17 cases (8%). No life-threatening cases were identified. Typical errors identified: documentation error, wrong infusion speed and prescription error or omission error. | This study helped provide important information about the rate and epidemiology of medication errors, emphasizing on the role of audit in enabling development of appropriate error-reducing strategies, particularly in the context of quality assurance in hospitals. |
| Ghaleb <i>et al.</i> 2009 UK | To evaluate what type of medication errors occur when prescribing and administering drugs by using quantitative and qualitative methods. | P, RE | DIFFERENT WARDS from 5 hospitals Two week data collection 2955 prescriptions were evaluated and 2249 administration of drugs were observed | -prescription -administration | 391 prescription errors (13.2%). Most typical errors regarding prescriptions were: insufficient prescription (missing something such as administration route), use of abbreviations and wrong dose. 429 administration errors. Most typical errors regarding administration were: preparing of the drug, wrong administration route with i.v. drugs and wrong timing. Significant difference regarding prescription errors between wards was detected. Root causes should be analysed. Observed medication errors were compared to error registry and when observing, more medication errors were detected. Hence, errors are under reported. | Prescribing and medication administration errors are not uncommon in paediatrics, partly as a result of the extra challenges in prescribing and administering medication to this patient group. The causes and extent of these errors need to be explored locally and improvement strategies pursued. |

| | | | | | | |
|---|--|--------------|--|-----------------------------|--|--|
| <p>Fernández-Llamazares <i>et al.</i> 2013 Spain</p> | <p>To describe what sort of prescription errors pharmacists can detect and how these errors could be prevented and how to recognise most common error types.</p> | <p>P, D</p> | <p>DIFFERENT WARDS Eight hospitals included.</p> | <p>-prescription</p> | <p>646 interventions related to quality of the prescription were included. 41.2 % concerned manual prescribing systems, and 58.8 % electronic prescribing systems. In interventions concerning prescribing errors, 212 different drugs were involved, mainly belonging to the group of anti-infectives. Main prescription errors are dosing errors (49.3 %). 51.9 % (306 cases) were considered significant, 26.3 % (155 cases) of minor significance, 19.8 (117 cases) were clinically serious and 2.0 % (12 cases) were potentially fatal. The impact of accepted interventions showed that 64.7 % had a significant impact on patient health outcome, highlighting 1.1 % with a highly significant impact. The activity level of the paediatric clinical pharmacists was highly variable, with a median of 0.014 interventions/bed-day during the data collection period.</p> | <p>In view of the importance of the dosing errors in the prescription phase, and the clinical relevance of the errors detected, it seems to be necessary to implement measures as the development of decision support systems for paediatric dosing and strengthen the presence of pharmacists as a key element in preventing prescribing errors from reaching patients, thus ensuring that children receive effective, safe and efficient drug therapy.</p> |
| <p>Manias <i>et al.</i> 2014 Australia</p> | <p>To describe the prevalence and quality of medication errors and predisposing factors in hospital.</p> | <p>R, RE</p> | <p>ALL WARDS during 4 years</p> | <p>-all types of errors</p> | <p>2753 medication errors were reported. The most common errors were: dose calculated wrong, too high dose given, omission of a drug and wrong technique regarding administration of i.v. drugs.</p> | <p>The importance of communication is relevant especially when child is transferred to another medical ward.</p> |

| | | | | | | |
|--|---|--------------|---|----------------------------------|--|--|
| Nieman <i>et al.</i> 2014 Germany | To prevent medication errors in paediatric wards. Pharmacists monitored drug handling by nurses prior to and following each intervention step. | I | One paediatric ward | -errors related to drug handling | The number of patients who were subjected to at least one medication error in drug handling decreased from 38/43 (88%) to 25/51 (49%) following the third intervention, and the overall frequency of errors decreased from 527 errors in 581 processes (91%) to 116/441 (26%). The issue of the handout reduced medication errors caused by knowledge deficits regarding, for instance, the correct “volume of solvent for IV drugs” from 49-25%. Interventions reduced medication errors significantly. | Paediatric drug handling is prone to errors. A three-step intervention effectively decreased the high frequency of medication errors by addressing the diversity of their causes. |
| Rinke <i>et al.</i> 2008 US | To describe the prevalence and quality of prescription medication errors in medical wards and clinics in order to develop medication safety. To discover whether a clinical pharmacist at the medical wards would be useful in reducing medication errors. | R, Q, QN, RE | DIFFERENT WARDS. Data from 2005 during 17 days and 6 months periods. | -prescription | 47/ of 377 (12.5%) in-house orders and 37/ of 191 (19.4%) individual charts contained at least 1 error: 4 (1.1%) orders contained an incorrect dose, 41 (10.8%) were written incorrectly and 2 (0.5%) contained an incorrect dose and were written incorrectly. Drugs most often associated with medication errors were morphine, acetaminophen, ibuprofen (in the medical wards) and amoxicillin, ibuprofen, diphenhydramine (in clinics). | Prescribing errors are common in both written in-house orders and ambulatory prescriptions in a PED. Targeting safety interventions toward groups with less practice in prescribing paediatric doses and re-educating groups on safe medication writing techniques could decrease this error rate. |
| Shaw <i>et al.</i> 2012 US | To describe medication errors in PICUs. Develop a standardized system for the analysis of medication errors. | R, Q, RE | 18 PICUs and medication errors in those were collected between 2007 and 2008. | -all types of medication errors | 597 medication errors reported. Most common type of medication errors were wrong dose (39%), wrong medication (17%) and delayed or missed dose (16%). Most commonly involved medicines were anti-infectives (25%), analgesics (21%), intravenous fluids (12%) and respiratory (11%). 13% of recorded errors were associated with non-fatal harm to the patient. | Reporting by the system revealed valuable data across sites on medication categories and potential human factors. Harm was infrequently reported. Our analyses identify trends and latent systems issues, suggesting areas for future interventions to reduce paediatric medication errors. |

| | | | | | | |
|--|---|------|--|---------------------------------|---|--|
| Sears <i>et al.</i> 2012 Canada | To define what factors contribute to medication errors. | S | DIFFERENT WARDS from different sections of Canada. . | -all types of medication errors | 127 potential and 245 actual medication errors reported. Most commonly reported medication errors: wrong timing of the drug, wrong dose, and wrong medicine. | The next step is to explore how errors occur within the entire medication delivery process. The lack of standardization has lead to a paucity of comparability across sites and studies that in turn have reduced the advancement of research findings in this area. |
| Snijders <i>et al.</i> 2007 Netherlands | To evaluate reported medication errors and to identify what types of errors are most risky at NICU. | P, S | 10 NICUs and one ICU ward where medication error reports were evaluated during 7 months. | -all types of medication errors | 4846 incident reports (not all related to medication errors) that entailed narrative part as well as multiple choice questions regarding clinical significance of the error. Reported incidents concerning medication dosing errors pose high risk to patients in the NICU. | Incidents occur much more frequently in our NICUs than previously observed, and their impact on patient morbidity is considerable. Reported incidents concerning mechanical ventilation, blood products, intravascular lines, parenteral nutrition, as well as medication dosing errors pose the highest risk to patients in the NICU. |

Prospective study=P, Retrospective study=R, Observation study=O, Explorative study=E, Registry study=RE, Intervention study=I, Survey study=S, Descriptive study=D, Qualitative study=Q, Quantitative study=QN, GEN=general paediatric ward, PICU=paediatric intensive care unit, NICU=neonatal intensive care unit, ICU=intensive care unit, ONC=oncology patients/ward

Two studies identified antimicrobial errors as one of the most common medication errors of all the drug classes used [28, 30]. More specific information regarding antimicrobial errors in paediatrics is definitely needed since antimicrobials, together with analgesics, are the most frequently consumed drugs in hospitals.

2.4. PRUDENT USE OF ANTIMICROBIALS

2.4.1. RESISTANCE TOWARDS ANTIMICROBIALS

Pathogens, such as bacteria, viruses and fungi, can develop resistance towards antimicrobials [77]. Resistance can be developed by multiple mechanisms, and as a result of such development the pathogens are either partly or entirely resistant to given antimicrobials. Numbers of resistant pathogens are unfortunately constantly increasing, which necessitates the prudent use of antimicrobials. According to the Centers for Disease Control and Prevention (CDC), the most threatening resistant bacteria are carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL-producing *Enterobacteriaceae* (extended-spectrum β -lactamases), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Pseudomonas aeruginosa* and multidrug-resistant *Acinetobacter* [78]. Due to these threats, in 2017 the WHO published a list of bacteria for which new antibiotics are urgently needed to combat the infections. All of these so-called high-priority bacteria (*Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*) are carbapenem-resistant and *Enterobacteriaceae* are likewise ESBL-enzyme producing [78]. In general, this means that beta-lactam antibacterials are no longer effective against these resistant pathogens. All of these critical, high-priority bacteria can cause lethal invasive infections. Hence, the growing resistance is alarming since carbapenems and third-generation cephalosporins have been the most efficient drugs against multi-drug resistant bacteria. ASPs are being implemented in order to tackle the alarming growth of antimicrobial resistance.

2.4.2. ANTIMICROBIAL STEWARDSHIP PROGRAMS IN HOSPITALS

Antimicrobial stewardship programs (ASPs) in hospitals are aimed at reducing the unnecessary use of excessively broad-spectrum antimicrobials in order to restrict these drugs to situations where they are the only effective treatment. Likewise, optimizing patient outcomes and minimizing the probability of adverse effects are a high priority. According to the CDC, the core elements of ASPs include the following: involving leaders, using physicians as leaders, appointment of pharmacists for developing and improving antimicrobial use, taking actions such as evaluating ongoing processes regarding antimicrobial therapies, monitoring the prescribing

and resistance of antimicrobials, reporting of antimicrobial use to healthcare professionals and educating healthcare professionals on resistance and clinicians on prescribing [80]. ASPs have been successful globally [81], and these programs have been applied in Finland as well, with a typical example being surveillance of antimicrobial resistance patterns [82].

The key factors regarding successful ASPs and interventions that improve appropriate use of antimicrobials have been investigated by multiple good-quality studies with large data or high-quality expert panels involved [83–91]. Davey *et al.* conducted a systematic review regarding antibiotic prescribing patterns and how inappropriate patterns could be influenced by using either restrictive techniques or enabling techniques [85]. Interventions with enabling techniques offering feedback for the prescriber were considered more effective compared to restrictive interventions only, such as controlled antimicrobial lists. Dellit *et al.* proposed a list of activities that could be prioritized depending on the institute at hand [86]. These elements include education, guidelines and clinical pathways, antimicrobial order forms, combination therapy, streamlining or de-escalation of therapy, dose optimization and parenteral to oral conversion. Systematic review by Schuts *et al.* offers an evidence-based list on of key measures assuring the prudent use of antimicrobials [90]. This list includes five core elements: 1) empirical treatment according to local or national guidelines, 2) de-escalation of treatment, 3) parenteral-to-oral switch, 4) therapeutic drug monitoring and 5) restricted antimicrobial lists. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) introduced a process for common structure indicators for hospital ASPs [91]. They discovered that a functional ASP needs a suitable infrastructure, appropriate practice and policy measures, and monitoring and feedback elements in order to be effective. Regarding paediatric hospitals, a study by Nichols *et al.* introduced several core elements for paediatric ASPs and stated that pharmacists educated in infectious diseases and paediatrics should be involved in these programs as part of a multidisciplinary team [92].

2.4.3. MONITORING ANTIMICROBIAL CONSUMPTION IN CHILDREN'S HOSPITALS

Investigating and monitoring the consumption of antimicrobials in hospitals is necessary in order to encourage prudent use of these drugs. The use of broad-spectrum antibacterials is a potential problem. It causes selection pressure and may lead to increasing numbers of resistant pathogens. In addition, such use of antibacterials probably also causes difficult secondary infections [93, 94]. Similarly, local knowledge of the use of antimicrobials is crucial and allows us to implement necessary measures to support appropriate use of antimicrobials.

When investigating the consumption of antimicrobials, Defined Daily Doses (DDDs) can be used. DDD is the assumed average maintenance dose per day for

a drug used for its main indication in adults [95, 96]. Numerous studies have investigated the consumption of antimicrobials in hospitalized adult patients by using DDDs [97–100], but there are few studies in paediatric patients.

There are obvious obstacles when using DDDs in children, the most important being that the paediatric population is a very heterogeneous group with great variation in weight and age. Thus, comparing neonatal use with that of adolescents is very challenging. The DDDs may, however, be used to describe paediatric consumption of individual antimicrobials over a certain period of time in a setting where no major changes in the hospital clientele took place.

Measuring the consumption of antimicrobials is recommended by the WHO [101]. Monitoring of antibiotic use is also a prerequisite of local control of these pharmaceuticals. According to a Cochrane review, interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcomes [102].

Consumption of antibacterials in Finnish hospitals in adults and children has been relatively moderate when compared to other European countries [103]. The most commonly used group of antibacterials are beta-lactams, since they are well tolerated and efficient against several pathogens causing community-acquired paediatric infections such as pneumococci, meningococci and streptococci. In a recent study of 32 European paediatric hospitals, the most commonly used antimicrobials were ceftriaxone, ampicillin, cefuroxime and oral amoxicillin [104].

Whether or not the DDDs represent actual use of antimicrobials in paediatrics, i.e., prescription daily doses (PDDs), has been widely discussed. The PDDs of a drug give the amount of the drug that actually has been prescribed. DDDs represent the daily use of a drug for its main indication with its average dose. If the drug is used for other purposes besides its main indication or with another dose, it is not equivalent to the DDDs. One study suggests that there is a strong correlation between DDDs and PDDs [105]. However, others have concluded that there are differences between the two [106–108].

Despite these difficulties, many studies investigating the consumption of antimicrobials in DDDs in children [109–112] have been published. A review regarding ways of measuring antimicrobial consumption concluded that to date there are no ideal ways of measuring the consumption of antimicrobials in children [113]. Fortin *et al.* concluded that the most frequently used method of measuring antimicrobial consumption in paediatrics was the use of DDDs, which was applied by 42% of studies. Currently, the WHO does not recommend the use of DDDs as a measurement in children, but in practice this approach is commonly used since more accurate methods are not available [114]. Thus, there are no generally accepted DDDs for children, although some studies have suggested possible DDDs for different ages of children [115, 116].

At the moment, there is an obvious need for the development of novel means of measuring antimicrobial use in paediatric patients. One possible way of producing such data would be based on the weight of individual patients. The study by Porta *et al.* in 2012 (European ARPEC project) suggested age-appropriate DDDs for antibiotics, especially for neonates [115]. On the other hand, some studies suggest that adult DDDs in paediatrics may be equal with PDDs or higher [104, 117].

2.5. CONCLUSION

Based on the literature reviews and literature searches, there are a great deal of gaps regarding AMT in hospitalized children, both globally and locally in the Children's Hospital, Helsinki University Hospital. For many areas of interest, there are no studies conducted in paediatrics or the evidence is scarce (Table 8.).

Table 8. Current gaps regarding antimicrobial therapy (AMT) in hospitalized paediatric patients in literature and issues investigated by this thesis via four studies.

| Gap identified | Study addressing issue |
|--|------------------------|
| Globally no studies found on addressing evaluating the appropriateness of AMT for blood culture positive infections in paediatrics | Study I |
| Existing literature provides research on how to investigate antimicrobial consumption in children's hospitals but the Children's Hospital, Helsinki University Hospital has not investigated it's own antimicrobial use and resistance patterns in a concisely comprehensive manner over a long period of time | Study II |
| Existing literature provides some information regarding what antimicrobials are classified OL (off-label) in Finland vs. abroad, but information is needed about the current practices in the Children's Hospital, Helsinki University Hospital | Study III |
| Globally scarce information on antimicrobial medication errors in paediatrics | Study IV |

3. AIMS OF THE THESIS

The purpose of this study was to obtain detailed information on the use of antimicrobials in the tertiary Children's Hospital, Helsinki University Hospital, in order to support prudent, safe and efficient use of antimicrobials (Figure 4).

The aims of the studies were as follows:

- 1) To evaluate the appropriateness of AMT in children with blood culture positive infections (I)
- 2) To investigate the consumption of antimicrobials in the hospital in Defined Daily Doses (II)
- 3) To record the prevalence of off-label use of antimicrobials in neonates (III)
- 4) To analyse actual antimicrobial medication errors (IV)

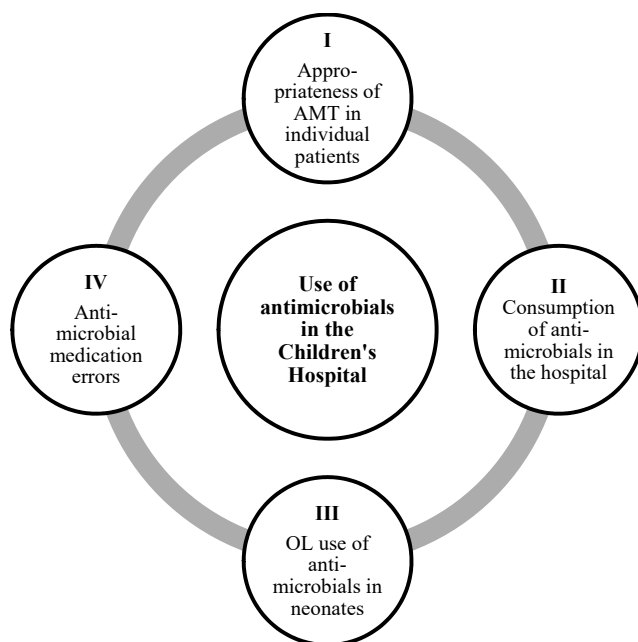


Figure 4. The studies (I-IV) included in the thesis. AMT=antimicrobial therapy, OL=off-label use.

4. MATERIALS AND METHODS

4.1. STUDY CONTEXT AND DESIGN

This study applied both prospective and retrospective data collection and both qualitative and quantitative methods, design and analysis of the data in order to investigate the use of antimicrobials in the Children's Hospital. Multiple data sources and different types of methods were applied in this thesis to provide a comprehensive and deep understanding of the appropriate use of these drugs (Table 9.).

Table 9. Materials and methods used in studies I–IV.

| Study | Study description | Data collection year(s) | Patient (N)/ Registry (RE) data | Data sources utilized | Methods and analysis |
|------------|---|--|---------------------------------------|---|------------------------|
| I | Analysis of patient records of patients with blood culture positive infections and AMT for the infection | 2005–2012 | N=149 | -Hospital infections database -Electronic patient records in Miranda program -WebLab laboratory results -Hand written patient records | R + QUAL |
| II | Surveillance of electronic records on antimicrobial consumption in Children's Hospital | 2003–2013 | RE | HUCH Hospital Pharmacy's electronic surveillance records on the use of antimicrobials | R + QUAN |
| III | 1) Point prevalence survey on OL AMT in all wards of the hospital 2) Electronic surveillance records on 20 most used antimicrobials in NICU 3) Analysis of patient records of NICU patients with blood culture positive infections and AMT for the infections | 1) 2014 (two days in spring) 2) 2009–2014 3) 2005–2014 | 1) N=99 2) RE 3) N=282 | 1) Patient records at the medical wards at the time of collection 2) Electronic patient records in Miranda program 3) Hospital infections database and electronic patient records in Miranda program on used antimicrobials in NICU | R + P + QUAL + QUAN |
| IV | Analysis of antimicrobial medication errors reported in patients from four wards (GEN, NICU, HEM-ONC and INF) | 2009–2014 | N=149 | HaiPro – electronic medication error reporting system | R + QUAL + QUAN |

AMT=antimicrobial therapy. OL=off-label. GEN=Paediatric kidney and transplantation ward NICU=neonatal intensive care unit, HEM-ONC=oncology and transplantation ward and INF=infectious diseases and observation ward. N=Number of patients included to the study, RE=Registry study with no patients included, R=Retrospective study, P=Prospective study, QUAL=Qualitative analysis, QUAN=Quantitative analysis.

4.2. STUDY POPULATIONS AND REGISTRY DATA

4.2.1. PATIENTS (I, III)

Two studies involved patients (Table 8). Both studies had patients with blood culture positive infections. In Study I, the patients were 0–17 years old and from all wards in the hospital. In Study III, two patient cohorts were used. The first cohort had patients 0–17 years old from all hospital wards, and the second cohort included only premature neonates.

4.2.1.1. *Antimicrobial therapy for children with blood culture positive infections (I)*

The Hospital for Children and Adolescents, Helsinki University Central Hospital, Finland, is a tertiary-care paediatric centre with 130 beds and approximately 100 annual blood culture positive BSIs. The most common blood isolates have been coagulase negative staphylococci (CONS) covering approximately 50% of all isolates. In order to obtain a more heterologous material for this analysis, five different groups of blood culture positive infections caused by different pathogens (*Staphylococcus aureus*, *Staphylococcus epidermidis*, streptococci, Gram negative rods and polymicrobial infections) were collected. This was done due to the natural occurrence of the causative bacteria in BSIs. At the Children's Hospital, infections caused by Gram positive bacteria are more common than infections caused by Gram negative bacteria (Figure 2). Since Gram positive bacteria are the causative agents in most cases, collecting Gram negative bacteria was also seen as important since they are generally more virulent and more complex to treat. The aim was to gather approximately 30 patients/group.

Data of the patients with blood culture positive infection was received from hospital infections registry database (Table 9.). Data from patients who suffered from infections caused by *S. aureus*, *S. epidermidis*, streptococci, Gram negative rods and polymicrobial infections were collected retrospectively in order of appearance from June 2012 backwards until year 2005. Due to the fact that *S. epidermidis* infections may often be caused by contaminants from the skin, patients with this bacterium were screened carefully in this study in order to include only those patients who had a blood culture positive infection (in most cases, fever and elevated leukocytes were present). Infections caused by fungi and anaerobes were uncommon and were therefore not analysed.

The following characteristics were recorded for each patient (if available): age, gender, duration of hospitalization, diagnosis and co-morbidities, weight, height, drug allergies, the use of antimicrobials 7 days prior to the diagnosis, the date of blood sample taken, the date of final blood culture results (i.e., when pathogen was

identified and the antibiogramme was given), leukocytes (neutrophils), empirically used antimicrobials, duration of empirical AMT days prior to receiving blood culture results and the antimicrobials selected after the blood culture result. Patients with no pathogens present in the final blood culture results were excluded from the study. The route of administration of antimicrobials was not recorded due to the fact that this study focuses on the choice of antimicrobial(s) and the appropriateness of AMT after final blood cultures have been received. For all antimicrobials used, the following were recorded: duration of AMT in days in total, antimicrobial used, dosing, formulation and duration of therapy individual antimicrobial. The surveillance period was from 7 days prior to receiving the positive blood culture to 30 days after the AMT for a healthcare-associated BSI was stopped or to the death of a patient.

4.2.1.2. Off-label use of antimicrobials in the Children's Hospital and in premature neonates (III)

This patient data consisted of patients of all ages from all hospital wards in order to investigate the prevalence of OL use in different patient groups, younger versus older children and patients with different co-morbidities (Table 9.). Thereafter, a prevalence study was conducted by selecting two random days during which the use of antimicrobials among all hospitalized patients was recorded in order to identify the prevalence of OL use. After the identification of the patients, the drugs used were recorded from electronic patient records. The patient data were collected by nurses and pharmacists on duty at the time and comprised patient's age, ward and antimicrobials used (active substance, dose and route of administration).

After the first study was conducted, a second study population was examined, consisting of premature neonates with a birth weight of less than 2000g who had blood culture positive infections (Table 9.). Blood culture positive infections were chosen because these infants were treated with antimicrobials. The list of eligible patients was retrieved from the hospital infections database. Patients were divided into four different weight categories based on Hack *et al.* [118]. All antimicrobials administered to these neonates during the first month (30 days) of life from 2005 to 2014 were recorded. Patients with insufficient data, e.g., cases where the antimicrobials used were not included in the patient records, were excluded. The data on the used antimicrobials were obtained from electronic patient records and included the individual drugs used and the duration of the AMT. It did not include, for example, the dosing of these drugs. Information regarding dosing, dosage form or route of administration was not available from the electronic records since electronic prescribing started at The Children's Hospital only in 2014. Thus, complete data on drugs, including dosing, have been available electronically from only 2014 onwards.

4.2.2. REGISTRY DATA (II, III, IV)

Three studies involved the use of registry data on either the consumption of antimicrobials or occurrence of antimicrobial medication errors at the hospital.

4.2.2.1. Consumption of antimicrobials in Defined Daily Doses (II)

This retrospective study investigated the consumption of antimicrobials in Defined Daily Doses, DDD according to the Anatomical Therapeutic Chemical (ATC)/DDD index defined by the WHO [118].

The antimicrobials included in this study were the following (according to Anatomical Therapeutic Chemical (ATC)/DDD index defined by WHO, 2010):

J Anti-infectives for systemic use:

Jo1 Antibacterials: Jo1A Tetracyclines, Jo1B Amphenicols, Jo1C Beta-lactam antibacterials, penicillins, Jo1D Other Beta-lactam antibacterials, Jo1E Sulfonamides and trimethoprim, Jo1F Macrolides, Lincosamides and streptogramins, Jo1G Aminoglycoside antibacterials, Jo1M Quinolone antibacterials, Jo1R Combinations of antibacterials, Jo1X Other antibacterials.

Jo2 Antifungals: Jo2AA Antibiotics, Jo2AC triazoles, Jo2AX Other systemic antifungals.

Jo5 Antivirals: Jo5AB Nucleosides and nucleotides excluding reverse transcriptase inhibitors, Jo5AD Phosphonic acid derivatives, Jo5AE Protease inhibitors, Jo5AF Nucleoside and nucleotide reverse transcriptase inhibitors, Jo5AG Non-nucleoside reverse transcriptase inhibitors, Jo5AH Neuraminidase inhibitors, Jo5AR Antivirals for treatment of HIV infections.

The data on the consumption of antimicrobials were collected from 2003 to 2013 from electronic surveillance records provided by Helsinki University Central Hospital (HUCH) pharmacy. Analysis was quantitative. The data regarding the days of hospital care were collected from HUCH electronic records. During 2003 and 2013, the days of hospital care (HD) varied annually between 30,226–39,930.

Electronic surveillance records did not allow us to differentiate enteral and parenteral use from antimicrobials that are available in both parenteral and enteral formulations. Therefore, enteral consumption was included in the study from drugs that have both enteral and parenteral formulations, such as trimethoprim, penicillins such as cloxacillin, fluoroquinolones, metronidazole, azoles and antivirals. Drugs with the same ATC code, such as amphotericin deoxycholate and liposomal amphotericin could not be separated and the total DDD describes them both.

4.2.2.2. Off-label use of antimicrobials in NICU (III)

At the same time as patient data collection was conducted for Study III (Table 9.), data were collected on the 20 most commonly used antimicrobials in the NICU from 2009 to 2014. The data regarding antimicrobial consumption in NICU was available from 2009 onwards. The data were obtained from the hospital's electronic registry of antimicrobial consumption in DDDs.

4.2.2.3. Medication errors and HaiPro reporting system (IV)

Medication safety in the Children's Hospital was investigated by using registry data on reported medication errors. HaiPro is a web-based tool for anonymous and voluntary reporting of patient safety incidents [120]. HaiPro is used in Finland in over 200 social service and healthcare organizations of various sizes, from small healthcare centres to entire hospital districts.

When a medication error occurs, healthcare professionals are advised to report the errors. The following factors are obliged to be reported when using the HaiPro system: reporter's unit, incident time and date, reporter's occupation, incident nature (near miss/adverse event) and incident description. In addition, there are also open questions about why the reporter thinks the error occurred and what sort of measures can be introduced in the future to prevent these types of errors.

In the Children's Hospital, the HaiPro reporting system has been in use from 2007 or 2009, depending on the ward. Initially, errors were reported via paper forms. In 2009, a digital HaiPro database was deployed in the hospital. From the launch of the reporting system to 2014, more than 2000 medication errors were reported.

Errors were analysed from the following departments: general paediatrics and transplantation ward (GEN), neonatal intensive care unit (NICU), oncology and haematology ward (HEM-ONC) and infectious diseases ward (INF).

4.3. METHODS

4.3.1. EVALUATING THE APPROPRIATENESS OF ANTIMICROBIAL THERAPY IN CHILDREN WITH BLOOD CULTURE POSITIVE INFECTIONS (I)

In this study, the appropriateness of targeted antimicrobial therapy was evaluated. The main focus of the study was the use of antimicrobials during the 72-hour window of time immediately after the final data on a positive blood culture was provided by the microbiology laboratory. Thus, the medical doctor(s) in charge was allowed 72 hours to respond to the microbiological data. If necessary changes in AMT were not made during this given time period (of 72 hours), the targeted

AMT was considered inappropriate. The quality of the targeted AMT given to each patient was evaluated retrospectively by an expert panel of three medical doctors: one clinical microbiologist (MV) and two infectious diseases consultants (V-JA and HS). The decision of whether the AMT of a particular patient was inappropriate or not, was consensus-based. This study did not evaluate the initial empiric therapy.

When evaluating the quality of therapy for HCA BSI, the following demographic characteristics were taken into account by the panel: age, co-morbidities, causative pathogen/pathogens and the level of granulocytes. A leukocyte count of $< 1.0 \times 10^9/\text{L}$ was considered as neutropenia. In general, antimicrobials having a broader spectrum were allowed in the treatment of patients with neutropenia ($< 1.0 \times 10^9/\text{L}$) compared with patients with normal white blood cell counts.

Inappropriate targeted AMT was divided in two categories: 1) the isolated pathogen was resistant to the selected antimicrobial(s), or 2) the isolated pathogen was either treated with an antibiotic with suboptimal efficacy or the pathogen was treated with overly broad-spectrum agents. Each patient was categorized into one category according to only the clinical significance of the inappropriateness of AMT. If the patient received both type 1 and type 2 inappropriate AMT, the patient was categorized into both of these categories. Analysis used in the study was both quantitative and qualitative.

Blood cultures were taken whenever an invasive infection was suspected. Blood culture samples were incubated in the BacT/Alert automated blood culture system (Biomérieux, France). Antibiotic susceptibility testing was performed using the disk-plate diffusion method and interpreted according to CLSI breakpoints (2005–2010) and EUCAST breakpoints (2011–2012). Data from the pro-forma were routinely entered into Microsoft Access (Microsoft Corporation, Redmond, WA; www.microsoft.com) and fully anonymised prior to analysis with Stata v.11.0 TM (Statacorp, College Station, Tx, US; www.stata.com). Patients with a minimum of two different pathogens detected in one blood culture sample were assigned to the polymicrobial pathogen group.

Hospital-acquired bacteremia was determined according to the classic CDC criteria, where laboratory-confirmed bloodstream infection is LCBI. LCBI is equivalent to this study's determination of HCA BSI.

The study was reviewed and approved by the local paediatric Ethical Committee.

4.3.2. MEASURING THE CONSUMPTION OF ANTIMICROBIALS (II)

In Study II, the change (in percent) in the consumption of antibacterials was calculated by using linear function over the consumption of antimicrobials from 2003 to 2013. This approach was in use when the drug had been used throughout the entire surveillance period (i.e., 2003–2013). If the consumption of a drug started later than 2003, the change in percentage was calculated by the year the drug use was initiated, for example, the use of micafungin was initiated in 2010. Electronic surveillance records did not allow the use of the individual ages of the children treated during the study period. Similarly, data on individual weights were not available. Hence, this study did not investigate the use of antimicrobials in children by using age-specific bands.

This retrospective registry study did not require the approval of the local ethical committee.

4.3.3. INVESTIGATING OFF-LABEL USE OF ANTIMICROBIALS IN FULL-TERM AND PRETERM NEONATES (III)

In Study III, labelled drug use was determined according to the product label [121]. SmPC is a legal document approved as a part of the marketing authorization for each drug. The SmPC is the basis of information for the healthcare professional on how to use the drug. Its information is updated throughout the life-cycle of the product as new data emerge [122]. Off-label (OL) drug use was determined as follows: the prescribed antimicrobials were determined as either labelled or OL use in relation to weight only. Age was not taken into account. The cumulative use of various antimicrobials was calculated in DDDs in NICU from 2009 to 2014. DDDs were based on adult DDDs. There are no DDDs defined for paediatric patients [123].

The retrospective registry study did not require an approval of the local ethical committee, otherwise study III was reviewed and approved by the local paediatric Ethical Committee.

4.3.4. ANALYSING ANTIMICROBIAL ERRORS (IV)

The occurrence of antimicrobial (antibacterial, antifungal and antiviral) medication errors in June 2009 to December 2014 was analysed retrospectively in all wards except the NICU, where the data were available from the year 2010. A medication error was defined as following: an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient [76].

Complete HaiPro data was received from the GEN, HEM-ONC and INF departments. With NICU, partial data were collected retrospectively from the HaiPro registry by nurses working in NICU.

Statistical analysis was qualitative and quantitative.

The study was reviewed and approved by the local paediatric Ethical Committee. Patients and caregivers cannot be identified from the HaiPro reports.

4.4. STATISTICAL ANALYSIS

In majority of the studies, qualitative and quantitative analyses were applied and the studies were descriptive in nature (Table 9.). For these studies, basic percentage calculations and ratios were utilized. In the OL antimicrobial use study (III), statistical analysis was conducted by using a logistic regression model fitted for OL usage with categorical birth weight as the predictive explanatory variable using R software [124]. Odds ratio, confidence interval (CI 95%) and p-value were also calculated.

5. RESULTS

5.1. EVALUATION OF ANTIMICROBIAL THERAPY OF BLOOD CULTURE POSITIVE HEALTHCARE-ASSOCIATED INFECTIONS IN CHILDREN (I)

5.1.1. PATIENT PROFILES AND EPIDEMIOLOGY

In total, 149 patients with blood culture positive infections with different types of causative pathogens were included (Table 10.). From these patients, 72/149 (48%) infants were either term or preterm neonates (≤ 28 days of age), the age of 24/149 (16%) children varied between 29 days and 1 year, the age of 39/149 (26%) infants was between 1 and 12 years, and 14/149 (9%) paediatric patients were between the ages of 12 and 17 years.

Table 10. Demographic data of the selected patients with HCA-bloodstream infections (n=149).

| Pathogen group/ co-morbidities | Patients/ pathogen group | Full-term neonates (< 28 days) | Premature neonates (born < 37 weeks old) | Patients with malignancies | *Surgical patients | ^Other co-morbidities |
|-----------------------------------|--------------------------|--------------------------------|--|----------------------------|--------------------|-----------------------|
| | Patients, n (%) | Patients, n (%) | Patients, n (%) | Patients, n (%) | Patients, n (%) | Patients, n (%) |
| <i>Staphylococcus aureus</i> | 25 (17) | 3 (12) | 6 (24) | 5 (20) | 8 (32) | 3 (12) |
| <i>Staphylococcus epidermidis</i> | 33 (22) | 1 (3) | 8 (24) | 12 (36) | 10 (30) | 2 (6) |
| Streptococcal species | 30 (20) | 18 (60) | 4 (13) | 5 (17) | - | 3 (10) |
| Gram negative bacteria | 38 (26) | 8 (21) | 14 (37) | 3 (8) | 9 (24) | 4 (11) |
| Polymicrobial infections | 23 (15) | 1 (4) | 9 (40) | 12 (52) | 1 (4) | - |
| Total | 149 (100) | 31 (21) | 41 (28) | 37 (25) | 28 (19) | 12 (8) |

*Surgical patients were patients who had undergone surgery during the same hospital admission as having BSI. ^Other co-morbidities were defined as patients with co-morbidities that could not be classified to any of the given categories.

The organisms of the streptococcal cohort were the following: *Streptococcus agalactiae* (GBS), (18/30, 60%), *Streptococcus viridans* (7/30, 23%), *Streptococcus pyogenes* (3/30, 10%), *Streptococcus pneumoniae* (1/30, 3%) and *Streptococcus salivarius* (1/30, 3%). All of the children infected by GBS were neonates. The staphylococcal cohorts consisted of patients infected either with *Staphylococcus aureus* (n=25) or *Staphylococcus epidermidis* (n=33). *S. aureus* was the most common pathogen isolated from surgical patients (8/25, 32%), and *S. epidermidis* was most frequently found in patients with malignancies (12/33, 36%). No MRSA infections were recorded.

The Gram-negative cohort consisted of the following: *Escherichia coli* (19/38, 50%) followed by *Klebsiella pneumoniae* and *Klebsiella oxytoca* (6/38, 16%), *Pseudomonas aeruginosa* (4/38, 11%), *Enterobacter cloacae* (3/38, 8%), *Serratia marcescens* (2/38, 5%), *Citrobacter* (n=1), *Stenotrophomonas maltophilia* (n=1), *Sphingomonas paucimobilis* (n=1) and an unidentified *Enterobacteriaceae* strain (n=1). Two patients suffered from bacteremias that were caused by an ESBL strain of *E. coli*.

The causative microbes of the polymicrobial group were the following: Gram+ Gram+ (9/23, 39%), Gram+ Gram- (9/23, 39%) and Gram- Gram- (5/23, 22%). In the case of two polymicrobial infections, three different pathogens were isolated simultaneously from the blood culture.

5.1.2. ADJUSTING THE EMPIRICAL USE OF ANTIMICROBIALS

The initial empirical antimicrobial therapy of 114 patients (77%) was changed during the study period within 3 days (72 hours) after receiving the final blood culture results. Empirical AMT was changed in 87% of cases in the polymicrobial infection group (20/23). In the other groups of pathogens, the treatments were changed as follows: *Staphylococcus aureus* 20/25 (80%), *Staphylococcus epidermidis* 26/33 (79%), Gram negative bacteria 27/38 (71%) and streptococci 21/30 (70%).

5.1.3. INAPPROPRIATE USE OF TARGETED ANTIMICROBIALS

AMT was considered totally inappropriate in three cases because the pathogen was resistant to all prescribed antimicrobials (Table 11.). In one case, an infection caused by oxacillin resistant *S. epidermidis* (MRSE) was treated with cloxacillin, and in another case MRSE infection was treated with cefuroxime and fluoroquinolone to which the strain was also resistant. One child received cefuroxime monotherapy for an infection caused by *Pseudomonas sp.*

5. Results

Table 11. Patients (n=3) who were prescribed entirely inappropriate therapy* due to resistance of the pathogen. Antimicrobial therapy (AMT) given 0–72 hours after identification of the pathogen and testing its antimicrobial sensitivity.

| Age | Co-morbidities | Isolate | Resistant to | AMT given |
|----------|---------------------------------|------------------------|--|-------------------------------|
| 3 months | left ventricular hypoplasia | <i>S.epidermidis</i> | oxacillin | cloxacillin* |
| 7 months | biliary atresia | <i>S. epidermidis</i> | clindamycin oxacillin levofloxacin | ceftriaxone* ciprofloxacin |
| 4 years | transposition of great arteries | <i>Pseudomonas sp.</i> | cefuroxime | cefuroxime* |

Ten patients received at least one antibiotic agent to which the pathogen was resistant (Table 12.). Five children with MRSE infections were treated with inefficient beta-lactams. Two patients with infections caused by *Klebsiella* received vancomycin. One child with an ampicillin-resistant *Citrobacter freundii* infection was treated with ampicillin. One child with a cefuroxime-resistant *Stenotrophomonas* infection was treated with cefuroxime, and another child with *E. coli* resistant to ciprofloxacin and penicillin was treated with ciprofloxacin and penicillin G.

Out of all 149 patients in the cohort, 13 (9%) received inappropriate AMT due to therapy that was considered to be of suboptimal efficacy against the pathogen. The most common cause for suboptimal use of AMT was the use of vancomycin in treating infections caused by methicillin-sensitive *S.aureus* (MSSA) (n=6) and in treating one patient with a methicillin-sensitive *St. epidermidis* (MSSE) infection. One MSSA infection was treated with penicillin G (and ceftriaxone) and one MSSA with both intravenous cefuroxime and oral cephalexin. One child with a penicillin-sensitive *Streptococcus viridans* was treated with meropenem, and another with an *Enterobacter cloacae* infection received cefuroxime monotherapy. Finally, one patient with a mixed infection caused by *E. cloacae* and *Enterococcus faecalis* received meropenem—an agent with suboptimal activity against the enterococcus. Another mixed infection caused by *Enterococcus faecalis* and an oxacillin-resistant *Staphylococcus sp* was treated with vancomycin, ampicillin and meropenem. Here, meropenem use was considered unnecessary.

Table 12. Patients (n=10) who were prescribed inappropriate therapy* due to resistance of the pathogen to one of the chosen antimicrobials. Antimicrobial therapy (AMT) given 0–72 hours after identification of the pathogen and testing its antimicrobial sensitivity.

| Isolate | N | Pathogen resistant to | AMT given |
|-------------------------------------|---|------------------------------------|--|
| <i>S. epidermidis</i> | 1 | oxacillin | cefuroxime* netilmycin |
| <i>S. epidermidis</i> | 1 | oxacillin | cefuroxime* clindamycin |
| <i>S. epidermidis</i> | 1 | oxacillin | cefuroxime* metronidazole |
| <i>S. epidermidis</i> | 1 | oxacillin | vancomycin meropenem* |
| <i>S. epidermidis</i> | 1 | oxacillin | teicoplanin meropenem* |
| <i>Citrobacter sp.</i> | 1 | ampicillin | penicillin G* netilmycin |
| <i>Stenotrophomonas maltophilia</i> | 1 | cefuroxime | cefuroxime* trimethoprim-sulfamethoxazole |
| <i>E. coli</i> | 1 | cefuroxime (ESBL) ciprofloxacin | penicillin G* meropenem ciprofloxacin* |
| <i>Klebsiella pneumoniae</i> | 1 | vancomycin | vancomycin* cefuroxime |
| <i>Klebsiella pneumoniae</i> | 1 | vancomycin | vancomycin* metronidazole cefuroxime |

Inappropriate AMT was found to be most common in the treatment of BSIs caused by *Staphylococcus aureus* (8/25, 32%) (Figure 5.). In contrast, inappropriate AMT was uncommon in infections caused by streptococcal species: only one patient, with ampicillin sensitive *Streptococcus viridans*, received inappropriate meropenem (1/30, 3%). Lack of de-escalation was a concern in the case of two patients: *S. viridans* infection was continued on meropenem treatment after the blood culture result was available. In addition, a polymicrobial infection (caused by *Enterococcus faecalis* and Staphylococcal species) received meropenem.

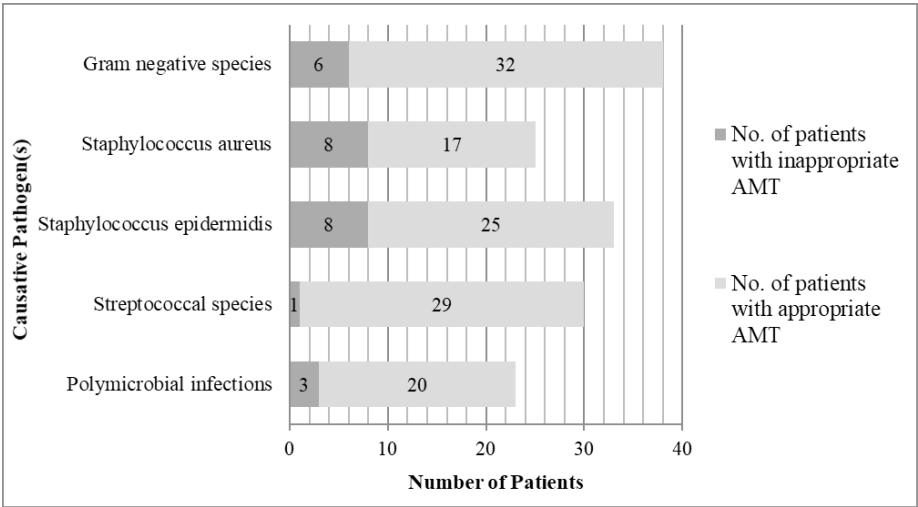


Figure 5. 26 patients (26/149, 17%) received inappropriate AMT 0–72 hours after receiving blood culture results.

5.1.4. OUTCOME OF ANTIMICROBIAL THERAPY

Mortality rate among the study patients was low. From the cohort of 149 patients, seven patients died (5%). Out of these seven patients, infection was the main cause of death in two cases only. Neither of these patients, however, died due to inappropriate AMT. The causes of death in these two cases were 1) duodenal atresia + sepsis and 2) neuroblastoma + sepsis.

5.2. ANTIMICROBIAL CONSUMPTION IN A TERTIARY CHILDREN’S HOSPITAL IN FINLAND (2003–2013) (II)

5.2.1. ALL ANTIMICROBIALS

The overall consumption of systemic antimicrobials (according to ATC classes and in DDDs) during the study period 2003–2013 was relatively stable (18,843–23,057 DDD) (Figure 6.). The days of hospital care (HD) varied annually between 30,226–39,930. The mean annual use of the antimicrobials was 20,800 DDDs, and the mean consumption per hospital days was 0.55 DDD/HD.

When the consumption of antimicrobials was calculated per patient days, the most frequently used pharmaceuticals were antibacterials (mean annual use 15,100 DDD and 0.40 DDD/HD) covering approximately 72% of all use. The second most commonly used group of drugs were antifungals at 18% of all use (3,700 DDD and

0.10 DDD/HD). Antivirals represented 10% (1,900 DDD and 0.05 DDD/HD) of all antimicrobial consumption.

Overall consumption of systemic antimicrobials in DDDs according to ATC classes divided by the days of hospital care (HD)/year in the Children's Hospital from 2003 to 2013 is shown in Figure 6.

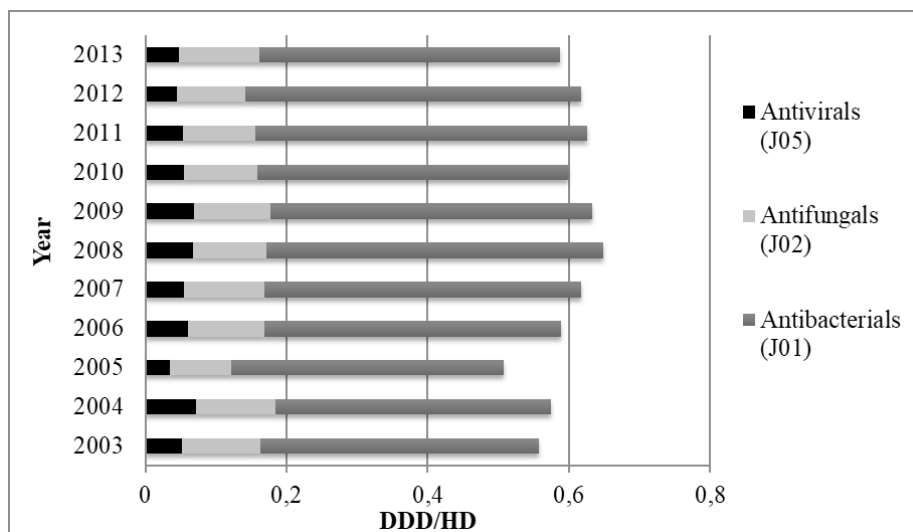


Figure 6. Overall consumption of antimicrobials in the Children's Hospital from 2003–2013 according to ATC classification and in defined daily doses (DDD) divided by the annual days of hospital care (HD).

5.2.2. ANTIBACTERIALS

From 2003 to 2013, the most frequently used group of antibacterials were beta-lactams, other than penicillins (J01D), including cephalosporins and carbapenems (annual consumption between 0.20–0.22 DDD/HD). The second most commonly used group of antibacterials were penicillins J01C (annual consumption between 0.070–0.105 DDD/HD).

Overall, when the early use (2003–2006) of penicillins, cephalosporines and carbapenems was compared to later use (2006–2013), a clear increase of 28%, 46% and 110% was recorded (Figure 7.). However, the use of aminoglycosides and vancomycin decreased during the same time periods by 61% and 41%, respectively.

A closer look at the drugs used against *Pseudomonas* infections revealed that the consumption of the antibacterials, such as carbapenems, piperacillin tazobactam and ceftazidime, increased constantly from 2003 to 2013 by 110%, 500% and 47%, respectively (Figure 8.). During the study period, the total number of invasive *Pseudomonas* infections, however, did not increase. Also, it was not possible to see any major differences in the drug resistance pattern of the isolates.

5.2.3. BETA-LACTAM ANTIBACTERIALS (PENICILLINS, CEPHALOSPORINS AND CARBAPENEMS)

The use of different beta-lactams is shown in Figure 7. Cefuroxime was the single most frequently used antibacterial agent, and its use grew steadily from 2003 to 2013. A clear change in consumption of ampicillin was seen 2006–2007 when compared to previous years. At the same time, the use of penicillin G was increased. Overall, from 2003 to 2013, the use of ampicillin decreased by 94% and the use of penicillin G increased by 100%. This shift from ampicillin to penicillin G took place due to changes in therapy recommendations given in 2006.

5.2.4. NON BETA-LACTAM ANTIBACTERIALS

Overall, the use of non beta-lactams did not change significantly from 2003 to 2013. The consumption of both aminoglycosides and vancomycin decreased by 61% and 41%, respectively, whereas the use of fluoroquinolones remained mainly the same.

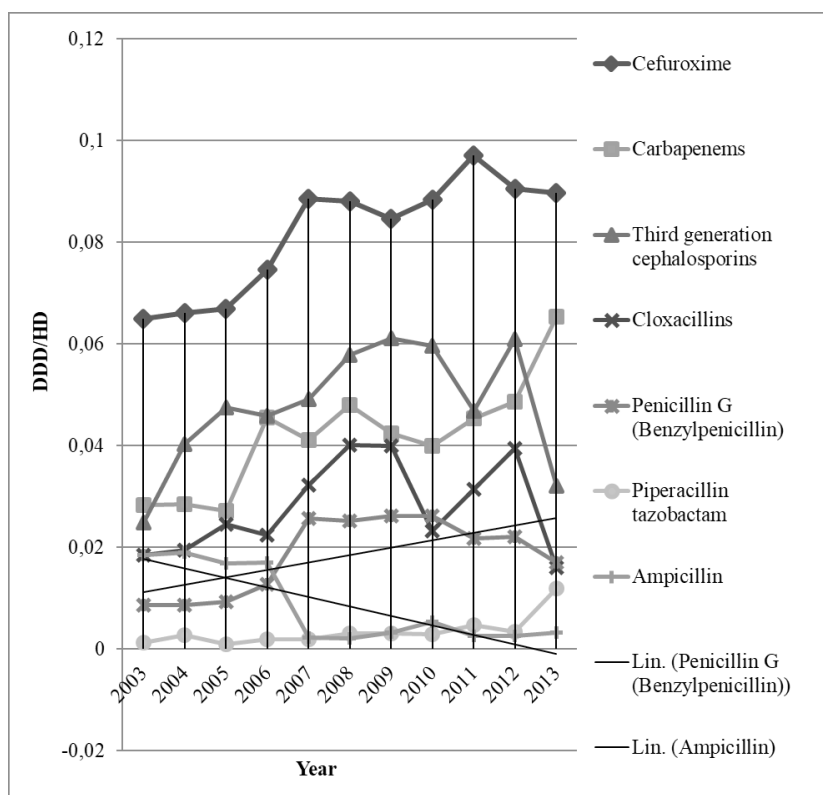


Figure 7. The use of beta-lactam antibacterials in the Children's Hospital from 2003–2013 according to ATC classification, penicillins (J01C), cephalosporins (J01DC, J01DD) and carbapenems (J01DH) in defined daily doses (DDDs) divided by the days of hospital care (HD)/year.

5.2.5. ANTI-PSEUDOMONAS ANTIBACTERIALS

In general, *Pseudomonas* species have been rare causes of invasive infections at the Children's Hospital. Nevertheless, the use of anti-pseudomonas drugs has grown. From 2003 to 2013, the use of aminoglycosides has decreased by 61%, whereas the use of piperacillin tazobactam, ceftazidime and carbapenems increased by 500%, 47% and 110% (Figure 8.), respectively.

The resistance of *P.aeruginosa* towards different antibacterials has somewhat increased over time. The antibiotic sensitivity of 435 *Pseudomonas aeruginosa* strains isolated from the blood or superficial samples taken from 2003 to 2013 were analysed (Figure 9.). Some year-over-year variation in resistance was seen. Overall, the resistance towards different antibacterials seemed to increase. For example, resistance towards piperacillin tazobactam reached its peak in 2011 when almost 40% of the isolates were resistant to the drug. Resistance towards meropenem and ciprofloxacin has likewise grown rapidly; in 2012, approximately 50% of the isolates were resistant to these drugs.

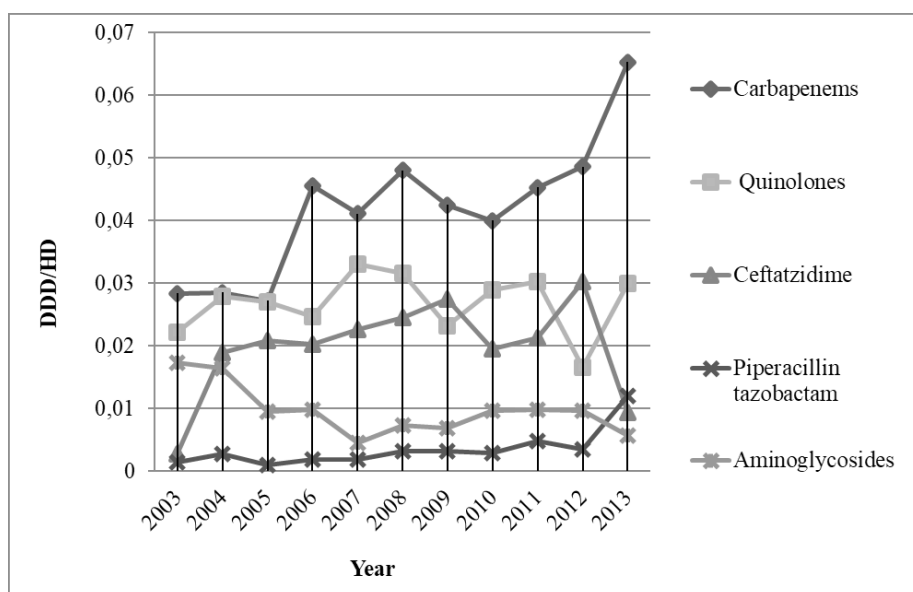
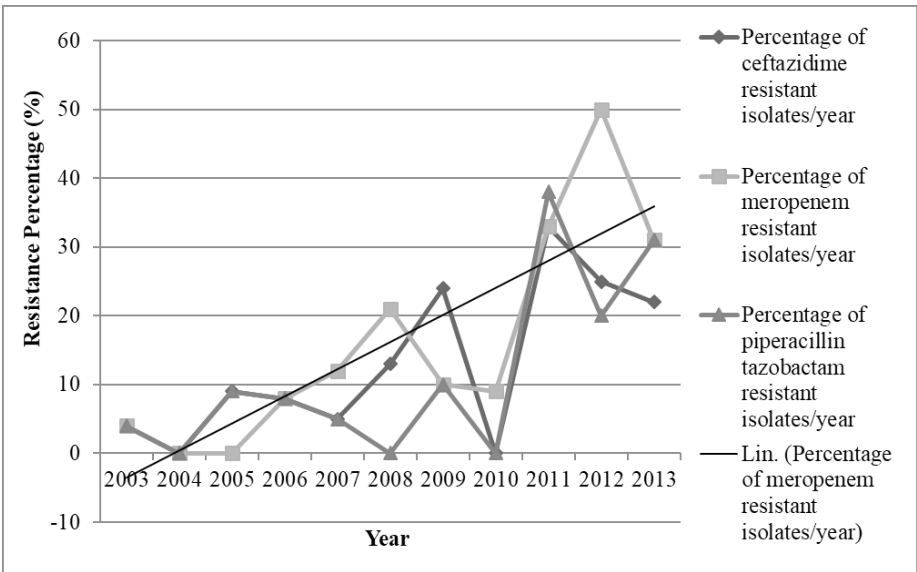


Figure 8. The use of anti-*Pseudomonas* antibiotics in defined daily doses (DDDs) according to ATC classes divided by the days of hospital care/year in the Children's Hospital from 2003–2013.

5. Results

A) The resistance % of *Paeruginosa* isolates towards beta-lactam antibacterials.



B) The resistance % of *Paeruginosa* isolates towards aminoglycosides and ciprofloxacin.

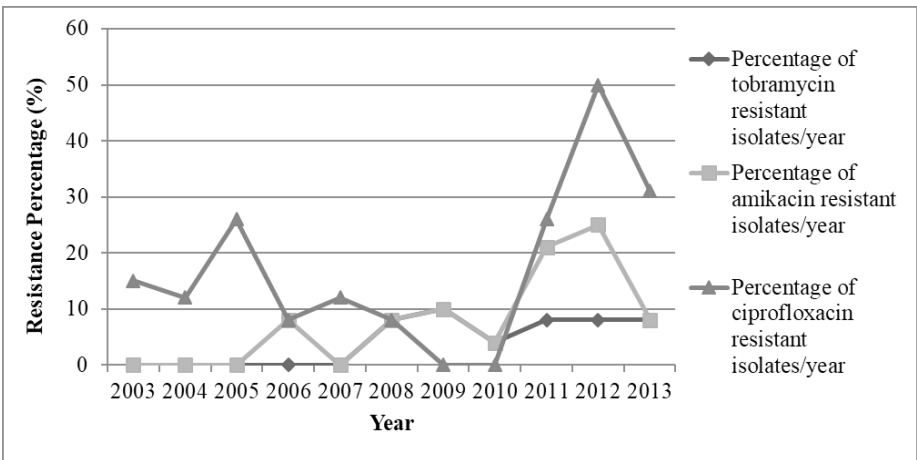


Figure 9. *Pseudomonas aeruginosa*, blood and pus isolates 2003–2013 in the Children's Hospital. One isolate/patient (the most resistant one). The number of isolates/year varied from 29–46, total N of isolates was 435.

5.2.6. ANTIFUNGALS

The overall consumption of all antifungals was somewhat decreased during the study period. From 2003 to 2013, the use of amphotericin and fluconazole decreased by 39% and 23%. On the contrary, during the same period, the use of voriconazole, posaconazole, caspofungin and micafungin increased by 34%, 295%, 134% and 67% (2010–2013), respectively (Figure 10.).

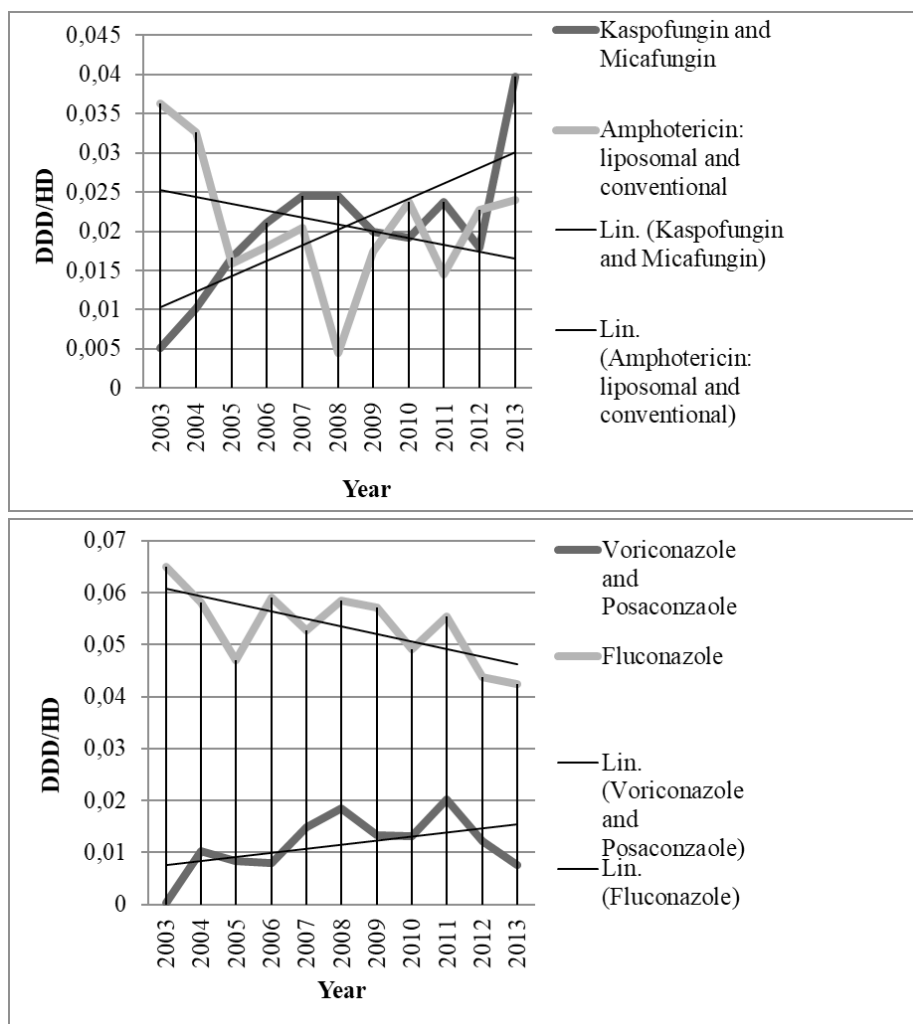


Figure 10. The use of antifungals in defined daily doses (DDDs) according to ATC classes divided by the days of hospital care (HD)/year in the Children's Hospital from 2003–2013.

5.2.7. ANTIVIRALS

The consumption of frequently used antivirals, such as valganciclovir, aciclovir and valaciclovir increased by 29%, 28% and 153%, whereas the use of ganciclovir decreased by 68% from 2003 to 2013.

5.3. OFF-LABEL USE OF ANTIMICROBIALS IN NEONATES IN A TERTIARY CHILDREN'S HOSPITAL (III)

5.3.1. OFF-LABEL USE IN THE HOSPITAL

Surprisingly, out of 99 patients included, only 6% (6/99) received off-label antimicrobials according to age (Tables 13. and 14.). Due to these results, more careful focus was given to premature neonates and NICU.

5.3.2. MOST FREQUENTLY USED ANTIMICROBIALS IN NICU

Measured in DDDs, meropenem was the most frequently used OL antimicrobial with 235 DDDs, while the total consumption of antimicrobials was 3547 DDDs (Figure 11.). Meropenem was followed by levofloxacin, rifampicin, piperacillin tazobactam, clindamycin, trimethoprim and ciprofloxacin, whereas the most commonly used labelled antimicrobials, measured in DDDs, were penicillin G (benzylpenicillin) with 1391 DDDs, vancomycin, metronidazole and netilmicin.

The most commonly used OL antifungals were amphotericin (43 DDDs) and caspofungin (42 DDDs), whereas fluconazole (581 DDDs) was used according to the product label. The antiviral most commonly used OL was valganciclovir (36 DDDs), whereas acyclovir (54 DDDs), ganciclovir (48 DDDs) and zidovudine (22 DDDs) were used according to the label in neonates.

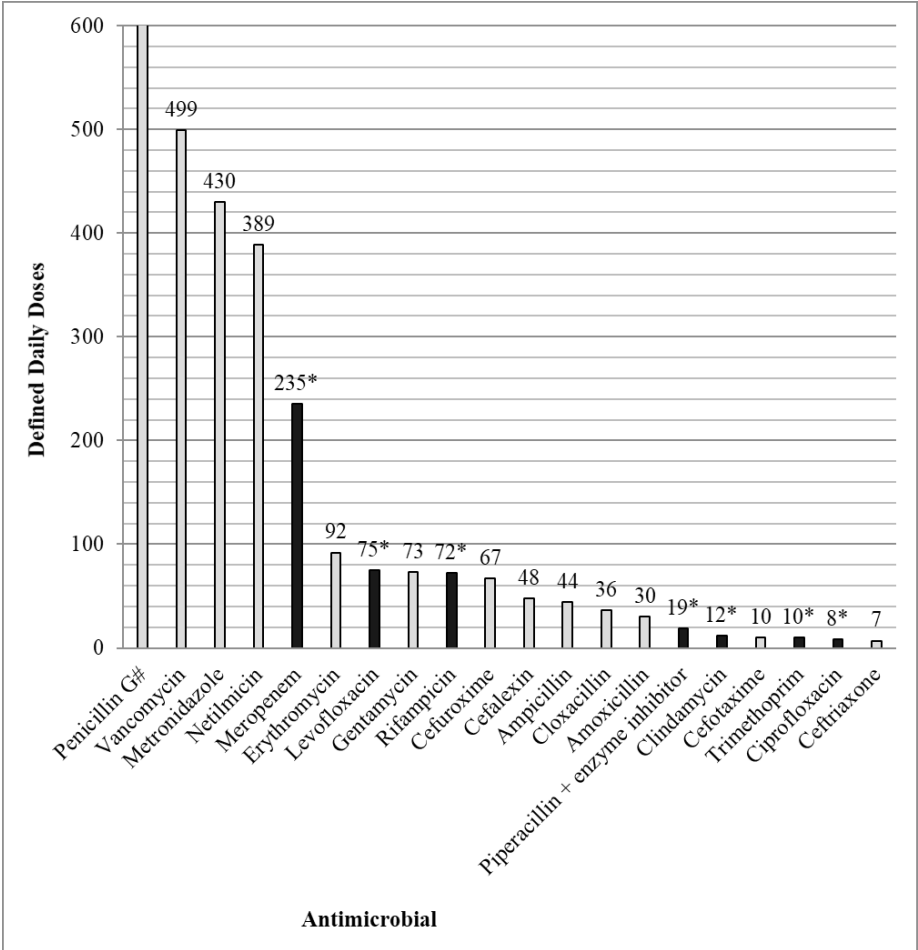
Table 13. Demographic data of the patients (N=99) and extent of off-label (OL) use according age in each age group. GEN=Paediatric kidney and transplantation ward, NICU=neonatal intensive care unit, PICU=paediatric intensive care unit, HEM-ONC=oncology and transplantation ward, INF=infectious diseases and observation ward.

| Medical ward | | | | | | | | |
|---------------------------|-----|---------|---------------------|-----------------------------|------|------------------------------|------|-----------|
| No of patients* (N=99) | GEN | Cardiac | Surgery and urology | Neonatal and infant surgery | NICU | Orthopaedic and traumatology | PICU | HEM-ONC |
| | 6 | 8 | 8 | 9 | 14 | 4 | 15 | 14 |
| | | | | | | | | INF |
| | | | | | | | | 21 |
| | | | | | | | | 6% (6/99) |

*Number of patients from different age groups: age < 30 days, n=15; < 30 days – 1 year, n=20; > 1 year – 12 years, n=51; > 12 years – 18 years, n=13

Table 14. The use of antimicrobials and prevalence of off-label (OL) antimicrobial use in 99 patients.

| Use of antimicrobials | Times used, n (%) (N=164) | Patients, n (%) (N=99) | Prevalence of OL use, n (%) (%) of patients | Antimicrobials used off-label according to age |
|-----------------------|------------------------------|---------------------------|--|---|
| Antibiotic in use | 136 (83%) | 97 (98%) | 3 (2%) | ciprofloxacin (given < 12 years old) trimethoprim (given < 6 weeks old) azithromycin (given < 1 year old) |
| Antifungal in use | 24 (15%) | 16 (16%) | 2 (8%) | posaconazole (given < 18 years old) |
| Antiviral in use | 4 (2%) | 4 (4%) | 1 (25%) | valganciclovir (given < 18 years old) |



#The number of DDDs for the use of Penicillin G is 1391.

Figure 11. The 20 most frequently used antimicrobials in NICU measured in Defined Daily Doses (DDD) between 2009 and 2014. Prevalence of off-label (OL)* use is shown with black bars. Prevalence of label use is shown with grey bars.

5.3.3. ANTIMICROBIAL THERAPY OF BLOOD CULTURE POSITIVE INFECTIONS IN PREMATURE NEONATES WITH BIRTH WEIGHT OF 400–2000G

There were 282 premature neonates with blood culture positive infections included. The number of eligible neonates varied from year to year between 22 and 37. Almost one-fifth of the patients (18%, 51/282) received at least one OL antimicrobial (Table 15.).

Table 15. Neonates weighing 400–2000g (N=282), and number of times antimicrobial was used off-label (OL) in 2005–2014 for blood culture positive infections.

| | | Weight group | | | | |
|--|--------------------------------|------------------|------------------|-------------------|----------------|-------------------|
| Weight | | 400–750g* | 751–1000g | 1001–1500g | 1501–2000g | 400–2000g |
| Patients with OL use / weight group, n | | N=14/49 (29%) | N=16/64 (25%) | N=18/123 (15%) | N=3/46 (7%) | N=51/282 (18%) |
| Times antimicrobial used/weight group, n | Meropenem | 13 | 14 | 16 | 2 | 45/282 (16%) |
| | Rifampicin | 3 | 2 | 4 | - | 9/282 (3%) |
| | Ciprofloxacin and Levofloxacin | 4 | 1 | 1 | - | 6/282 (2%) |
| | Linezolid | 1 | - | - | - | 1/282 (<1%) |
| | Clindamycin | - | 1 | - | - | 1/282 (<1%) |
| | Erythromycin | - | 1 | - | - | 1/282 (<1%) |
| | Piperacillin tazobactam | - | - | - | 1 | 1/282 (<1%) |
| | Caspofungin | - | - | 1 | - | 1/282 (<1%) |

On average, each neonate was given 1.3 antimicrobials OL. Meropenem was the most commonly used OL antibiotic, as 16% (45/282) of the neonates with blood-culture positive infections received this carbapenem. Other antimicrobials used without market authorization were rifampicin (3%, 9/282) and ciprofloxacin and levofloxacin (2%, 6/282). OL antimicrobial use varied according to weight group. An increase in birth weight was found to statistically significantly decrease the probability of OL usage (odds ratio=0.85 for 100g increase in birth weight, p-value < 0.001). The odds for OL use were higher the smaller the birth weight was (Figure 12.).

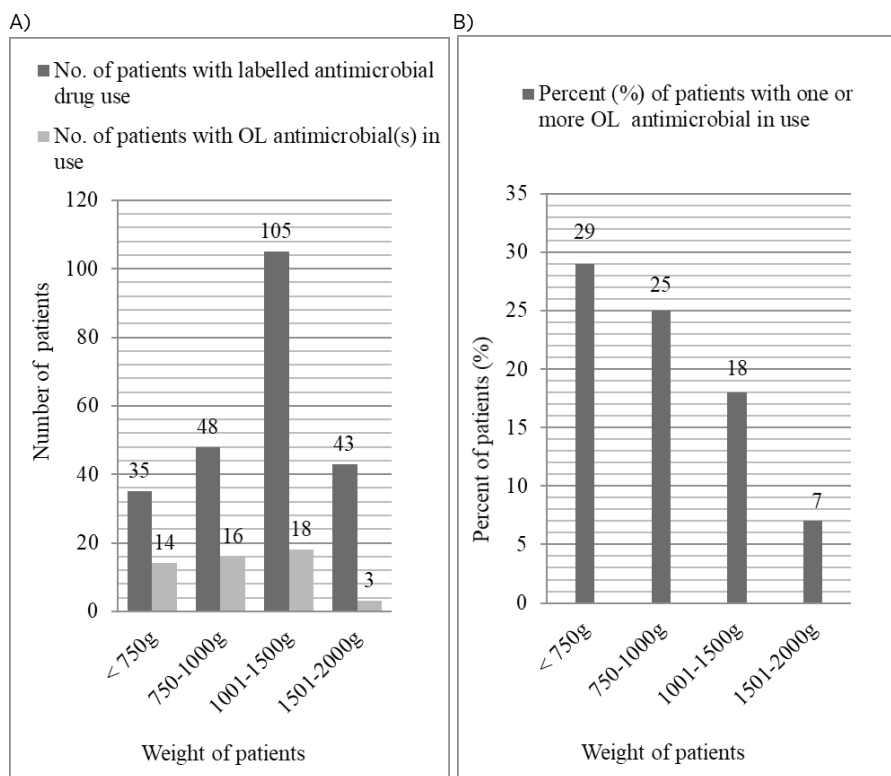


Figure 12. Neonates weighing from 400–2000g (N=282) with blood culture positive infections and the prevalence of off-label (OL) antimicrobial drug use. A) Number of patients with labelled/OL use of antimicrobials. B) Percent of patients with one or more OL antimicrobial used.

5.4. MEDICATION ERRORS RELATED TO ANTIMICROBIAL THERAPY IN A TERTIARY CHILDREN'S HOSPITAL (IV)

5.4.1. REPORTED ANTIMICROBIAL MEDICATION ERRORS

There were a total of 149 patients with 157 antimicrobial errors (1.1 errors/patient) between 2009 and 2014. The number of reported errors varied between departments with the highest number occurring in the INF ward and the lowest in the GEN ward (Table 16). These figures correlated with the total number of patients treated in these wards. Of the reported errors, 84% reached the patient (125/149). During the study period, there were on average 0.0017 errors reported annually/days of care. The annual number of reports increased over time. Thus, there were 23 patients at the beginning of the study period in 2010 (first full year) and 34 patients in 2014 who experienced antimicrobial medication error(s).

Most of the reported errors were related to administration (99/149, 66%), followed by prescription (12/149, 8%), transcription (8/149, 5%), preparation of the drug (6/149, 4%) and other (2/149, 1%). In 15% of the cases, the error type was not reported (22/149). Under administration errors, omission was most common error subtype (37/149, 25%), followed by a wrong dose prescribed, or prepared or given (36/149, 24%) and a wrong drug prescribed, or prepared or given (10/149, 7%).

Errors occurred more often with IV (intravenous) administered antimicrobials (116/149, 78%) when compared to PO (oral) administered antimicrobials (33/149, 22%).

Most errors took place with beta-lactams (Figure 13.). Drugs that were frequently involved in the errors were parenteral cefuroxime (15/157, 10%), penicillin G (15/157, 10%), parenteral vancomycin (13/157, 8%), netilmicin (12/157, 8%) and oral amoxicillin (12/157, 8%). Fluconazole was the most commonly reported antifungal involved in all antimicrobial errors (5/157, 7%). Aciclovir/valganciclovir were the most commonly reported antivirals (6/157, 4%). The antimicrobial-related and system-based antimicrobial medication errors that reached the patient can be seen in Table 17.

Table 16. Reported antimicrobial medication errors that reached or were near misses for the patients (N=149). GEN=Paediatric kidney and transplantation ward NICU=neonatal intensive care unit, HEM-ONC=oncology and transplantation ward and INF=infectious diseases and observation ward. * Preparation of the drug is done prior to administering the drug to a patient, it often involves dilution.

| | GEN | NICU | HEM-ONC | INF | All wards combined |
|---|--|---|---|--|---|
| Reported errors, n (%) | 24 (16%) | 44 (29%) | 28 (19%) | 53 (36%) | 149 (100%) |
| Errors reaching the patient, n (%) | 24/24 (100%) | 35/44 (80%) | 18/28 (64%) | 48/53 (91%) | 125/149 (84%) |
| Three most common IV-administered drugs involved in errors (errors, n). | ceftazidime (2), cefuroxime (2), meropenem (2) | netilmicin (11), penicillin G (8), vancomycin (8) | cloxacillin (4), ceftriaxone (3), ceftazidime (2) | cefuroxime (12), penicillin G (8), ceftazidime (4) | penicillin G (16), cefuroxime (14), netilmicin (11) |
| PO (oral)- administered drugs involved in errors (errors, n) | valganciclovir (3), trimethoprim (1), trimethoprim + sulphamethoxazole (1), ciprofloxacin (1), doxycycline (1) | - | fluconazole (2), voriconazole (2), aciclovir + nystatin (1), trimethoprim + sulphamethoxazole (1) | amoxicillin (12), cefalexine (3), fluconazole (3), aciclovir (1), voriconazole (1) | amoxicillin (12), fluconazole (5), valganciclovir (3), cefalexine (3) |
| Three most common error types and error types with IV-administered drugs (n) | omission (6), preparation of the drug* (4), wrong drug given (2) | wrong dose/dosing interval (13), preparation of the drug* (9), prescription (6) | preparation of the drug* (7), wrong dose/dosing interval (4), prescription (4) | omission (14), wrong dose/dosing interval (8), preparation of the drug* (4) | wrong dose/dosing interval (25), preparation of the drug* (24), omission (20) |
| Three most common error types and error types with PO-administered drugs (n) | omission (6), preparation of the drug* (1) | - | omission (2), transcription (2), wrong dose/dosing interval (2) | omission (11), prescription (3), wrong dosing interval (3) | omission (19), wrong dose/dosing interval (5), prescription (3) |

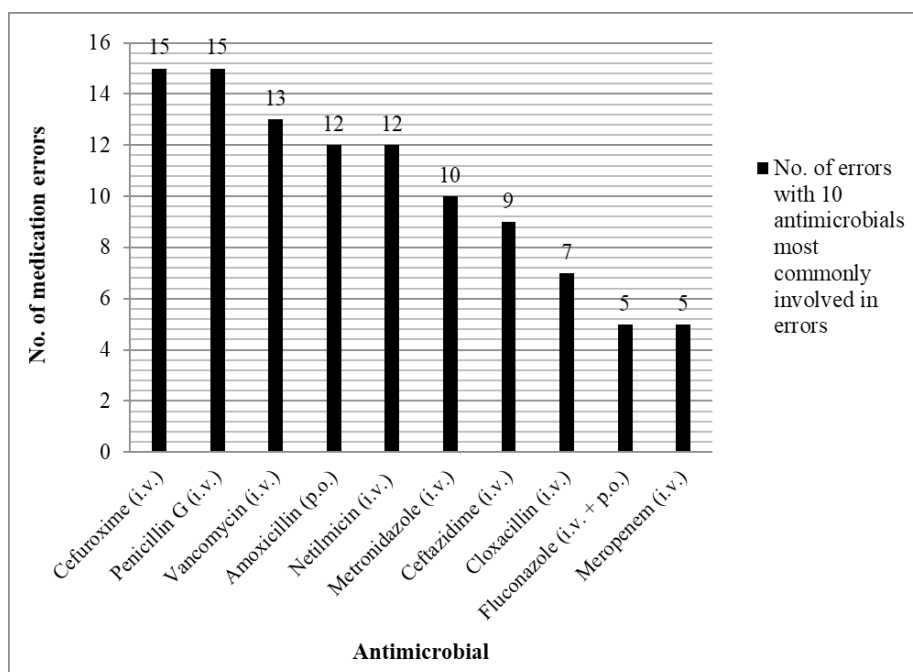


Figure 13. Antimicrobials involved in reported antimicrobial medication errors (N=157).

No fatal errors occurred. There were only two errors that were reported as clinically significant errors (2/149, 1%). The first incidence involved an interval that was too short for administering teicoplanin (Table 17) The interval was only 7 hours, whereas the recommended interval (after the therapeutic concentration is reached) is 24 hours. After identifying the error, the infusion was discontinued and safety tests were ordered. An exceptionally heavy workload at the NICU was reported as a contributing factor.

The second incident involved a very sick premature neonate who received a 10-fold overdose of vancomycin because the nurse forgot to dilute the drug. The neonate developed muscle spasms that were most probably related to the overdose. A sample for drug monitoring was taken, and furosemide was administered. Lack of experience in diluting pharmaceuticals was reported as a contributing factor.

Table 17. Identified system-based drug-specific antimicrobial medication errors that reached the patient.

| Drug(s) and prevalence of errors from all wards | Errors occurred/drug (N all errors =157, 100%) | Frequency of drug specific errors (N all errors =157, 100%) | Drug specific error | Drug and staff-related reasons for error |
|---|--|---|--|---|
| Amoxicillin | n=12 (8%) | 4/157 (3%) | Double dosing. | Two different oral liquid strengths, 50mg/ml and 100mg/ml. Nurses administered wrong strength. |
| Cefuroxime | n=15 (10%) | 4/157 (3%) | Ceftazidime was given instead of ceftriaxone. | Cephalosporins are known LASA* drugs. Nurses diluted and administered wrong drug. |
| Ceftazidime | n=9 (6%) | 1/157 (0,6%) | Ceftazidime was given instead of cefuroxime. | |
| Ceftriaxone | n=4 (3%) | | | |
| Ciprofloxacin | n=3 (2%) | 3/157 (2%) | Administering the drug with i.v. nutrition or calcium and formation of precipitation. | Lack of knowledge regarding ciprofloxacin's pharmacokinetics, many pharmacokinetic interactions. Nurses administered the drug inappropriately. |
| Fluconazole | n=5 (3%) | 1/157 (0.6%) | Was prescribed to a patient with prolonged QT-time. | Lack of knowledge regarding fluconazole's pharmacology and the patient's diagnosis. Medical doctor prescribed inappropriately. |
| Imipenem cilastatin | n=1 (0.6%) | 1/157 (0.6%) | The drug did not dissolve enough to the solvent and was partially given to the patient before discovering precipitation. | Not always easily soluble drug. Nurse did not dilute the drug carefully enough in order to assure it is appropriately dissolved to the diluent. |
| Teicoplanin | n=3 (2%) | 1/157 (0.6%) | Initiating therapy with loading doses that were given in too short intervals. | Exceptional dosing including loading doses when initiating therapy. Nurse administered the drug inappropriately. |

*LASA, look-alike and sound-alike.

5.4.2. ELECTRONICAL PRESCRIPTION PROGRAM CONTRIBUTING TO ERRORS

There was one error where, according to reporters, the computer program used was considered as a contributing factor. In this case, penicillin G was accidentally prescribed instead of vancomycin. The electronic prescription application used always recommends the most frequently used drugs for new patients. At the NICU, the most commonly used—and recommended drugs—were penicillin G and netilmicin. The patient who was supposed to receive vancomycin received penicillin G by mistake. The correct antibiotic was administered 4 hours too late. The nurse who reported this error suggested that such an application should be deleted from the program.

A second notable error, related to prescription application, was a case where ceftazidime and cloxacillin were prescribed in grams instead of milligrams. The prescriber was used to prescribing these drugs in milligrams, but the program transferred the milligrams to grams automatically since prescribing was according to grams instead of milligrams. Hence, a child was prescribed ceftazidime 800g three times daily and cloxacillin 400g four times daily. The error did not reach the patient.

5.4.3. CULTURE OF REPORTING MEDICATION ERRORS

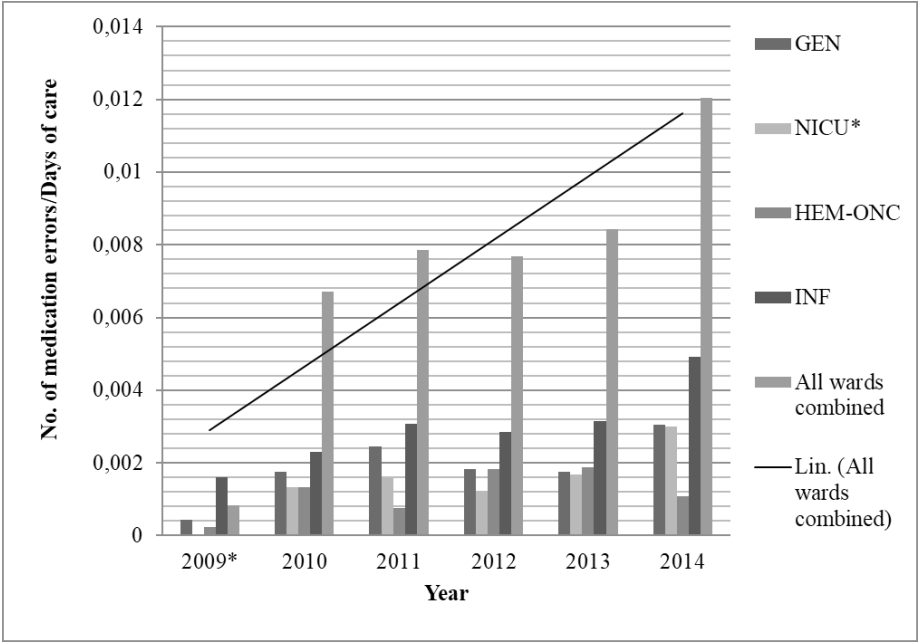
Overall, the reporting activity increased during the study period between June 2009 and 2014 (Figure 14.). Medication errors were most often reported in the INF ward.

In 87% (130/149) of cases, the report was made by a registered nurse. In 10% (15/149) of cases, the reporter was a pharmacist and in 3% (4/149) of cases, a medical doctor.

Full data, including the contributing factors reported as leading to medication error according to the reporter, were received from wards GEN, HEM-ONC and INF but not from the NICU. Primary contributing factors leading to errors were documented in 82% (86/105) of reports. Secondary contributing factors were documented in only 63% of the reports (66/105). There were some differences when comparing reporting activity between wards: reporting of the contributing factor was more common in GEN, 92% (22/24) and HEM-ONC, 27/28 (96%) than in INF, 69% (37/53).

The primary contributing factors for errors reported by the three wards (n errors=105) were related to environment, equipment and resources, 26% (27/105); way of acting and policy at the ward, 14% (15/105); and communication, 13% (14/105). Administration error was the most common error type (85/105, 81%). The primary contributing factor for administration error was reported in 78% of cases (66/85).

5. Results



* Data from NICU between 2010 and 2014.

Figure 14. Annually (June 2009 – December 2014) reported antimicrobial medication errors/Days of care. GEN=Paediatric kidney and transplantation ward NICU=neonatal intensive care unit, HEM-ONC=oncology and transplantation ward and INF=infectious diseases and observation ward.

6. DISCUSSION

6.1. ANTIMICROBIAL THERAPY IN BLOOD CULTURE POSITIVE INFECTIONS (I)

To our knowledge, Study I was the first study investigating the quality of AMT in children with HCA BSIs. This study focused on the vigilance of medical doctors in responding to microbiological results and on the appropriateness and quality of the targeted antimicrobial therapy. The applied approach of using a selected cohort consisting of different causative pathogens did not allow us to calculate the total magnitude of inappropriate use of antimicrobials of all blood culture positive infections at the Children's Hospital. It did, however, give us a general picture of which pathogens were most often targeted with inappropriate AMT.

Overall, we discovered that 77% of patients in the cohort had their empirical AMT changed after receiving the final blood culture results and 17% of these patients with HCA BSIs received inappropriate targeted AMT. The microbiological results were frequently either totally (2%) or partly ignored (17%) in the design of the subsequent treatment. Similarly, the choice of antimicrobial agents with suboptimal or overly broad-spectrum efficacy was not uncommon (9%). Surprisingly, inappropriate use of vancomycin in treating MSSA was the most frequent cause of inappropriate use. The second most common misuse was treatment of MRSE infections with beta-lactams. In all, beta-lactams were the most frequently misused group of antimicrobials. Inappropriate AMT was not associated to mortality.

A study by Willemsen *et al.* speculated that when evaluating incorrect use, the following parameters should also be taken into account: dosage, timing, administration and duration of AMT, rather than evaluating only the choice of the antimicrobial [66]. Due to the retrospective nature of Study I and the fact that we evaluated solely the choice of the antibiotics, we may assume that the frequency of inappropriate use of AMT was even higher than that reported. This is alarming since 17% of patients were receiving inappropriate AMT based only on the evaluation of the prescribed antimicrobial.

In Study I, vancomycin and carbapenems were the most inappropriately used antimicrobials. Two studies reported inappropriate use of vancomycin [61, 67]. Their main findings were similar to those of Study I, that one of the most frequently misused antimicrobials was vancomycin. The reason for this excessive use of vancomycin was not clear. One reason may be that many empiric therapy guidelines included vancomycin, but once the data on the pathogen were revealed, de-escalation was not executed. Hence, de-escalation of the drug should be conducted more often.

Increased provider awareness of drug-resistant CONS likely also increased the overall use of vancomycin. Similar findings have been published by Levy *et al.* [72]. A study by Di Pentima *et al.* investigated the impact of an ASP on vancomycin use in a paediatric teaching hospital and likewise identified excessive use of the drug [125]. The ASP reduced vancomycin utilization, prescribing errors and improved the quality of care and safety of paediatric patients.

Inappropriate vancomycin therapy in children can also occur when therapeutic drug monitoring (TDM) is not conducted or conducted incorrectly [125–130]. TDM is needed when using vancomycin due to the drug's nephrotoxicity [130]. Conducting TDM is particularly important when treating premature neonates and children with renal insufficiency or anomalies [132]. The problematic sides of conducting TDM include wrong timing of sampling (trough and peak concentrations) and completely neglecting the TDM [130]. It was discovered from Study I (unpublished data) that at the Children's Hospital in 44 children with BSI between 2006 and 2010 who were treated with vancomycin, 34% (15/44) of these patients' vancomycin TDM was not conducted. The duration of vancomycin therapy in these patients was more than 3 days. At the Children's Hospital, vancomycin TDM is recommended at minimum on the third and fifth days during therapy and after that if the therapy is longer than one week.

Regarding the prevalence of inappropriate AMT, the results of Study I (prevalence of 17%) were in line with other studies. The percentage of patients receiving inappropriate AMT varied (20–24%) in empirical AMT [59, 60, 61] and in targeted AMT (16–37%) [63–65]. Zaragoza *et al.* showed that inappropriate AMT was not associated with increased mortality [60]. This finding is in accordance with Study I where the inappropriate AMT was not associated with increased mortality. A plausible reason for this is that the infections in the Children's Hospital were rarely fatal due to the low virulence of the causative pathogens. Hence, most of the patients receiving inappropriate AMT suffered from infections caused by CONS. However, resistance towards antimicrobials is constantly increasing and the virulence of pathogens is expected to grow [35]. In addition, multiple studies show that inappropriate AMT is associated with increased mortality [58, 59, 63–65]. It is important that these factors be considered at the Children's Hospital when implementing an ASP.

Currently the Children's Hospital does not have an official ASP. Study I highlighted the importance of audits investigating the quality of AMT for different patient groups (neonates vs. older children) and different indications. Regular audits regarding clinical quality, safety and efficacy of prescribed and implemented AMT are being recommended by many studies as key components of ASPs [83–91]. As well, lack of TDM when using vancomycin was discovered. Utilizing ASP guidance on vancomycin therapy and monitoring at paediatric hospitals has been proven to decrease excessive vancomycin use and increase appropriate TDM [125]. Education

of healthcare professionals is of high importance as well in achieving prudent use of antimicrobials [83–91]. Study I demonstrated that medical doctors need to be further educated regarding appropriate prescribing of antimicrobials. There are numerous ASPs utilized in children's hospitals that can be further applied and developed for the Children's Hospital by a team of medical doctors, clinical microbiologists, nurses and clinical pharmacists [92, 133, 134]. According to the Infectious Disease Society of America and the Society for Healthcare Epidemiology of America, a modern and functional ASP should include infectious diseases physicians, clinical pharmacists with infectious diseases training, a clinical microbiologist and a hospital epidemiologist [135].

6.2. CONSUMPTION OF ANTIMICROBIALS (II)

A study of 32 European paediatric hospitals reported that the most commonly used antimicrobials were ceftriaxone, ampicillin, cefuroxime and oral amoxicillin [104]. The profile of antibiotic use in the Children's Hospital was very similar: beta-lactams were the most frequently used antibacterials.

From 2003 to 2013, there was a clear local rise in the consumption of penicillins and three major changes in the use of penicillins could be seen. The reduction in the use of ampicillin was obviously due to the change in guidelines on neonatal infections: penicillin G replaced ampicillin. This change was introduced because of the very low frequency of listeria infections. Recommendation of empiric therapy of early neonatal sepsis was changed from ampicillin (+ an aminoglycoside) to penicillin G (+ an aminoglycoside). Later on, a clear reduction in the consumption of penicillin G was noticed in 2011–2012. The reduced consumption of penicillin G took place at the same time as the pneumococcal conjugate vaccine was introduced to the national immunization program in 2010. A reduction of approximately 80% in the numbers of invasive pneumococcal infections was seen from 2011 to 2013 when compared to the pre-immunization era (data not shown).

A third significant change was seen in the use of piperacillin-tazobactam (PIP-TAZ) in 2012. This increase was due to new recommendations in the empiric treatment of sepsis in neutropenic patients. PIP-TAZ monotherapy replaced the previously used combination of ceftazime+cloxacillin in the treatment of patients with neutropenia and sepsis.

The increased use of carbapenems was the most prominent finding of Study II. This change has been reported by other European countries and hospitals in both adults and children [104, 117]. One reason for this has been that oncologists have become more concerned about infections caused by *Pseudomonas* and other multiresistant gram negative bacteria. Hence, guidelines were updated, and previous empiric therapy with a combination of cephalosporins and aminoglycosides was

replaced by either carbapenems or piperacillin tazobactam. The same practice has taken place in other Scandinavian countries [136]. On the other hand, the use of other anti-*Pseudomonas* drugs (aminoglycosides, ceftazidime, fluoroquinolones) did not increase significantly from 2003 to 2013.

The increased use of carbapenems should, however, be carefully evaluated. The overuse may induce an increase in numbers of carbapenem-resistant bacteria [137]. Other disadvantages associated with the use of the carbapenems may be an increased number of fungal infections. In addition, carbapenems are active against several anaerobic bacteria of the gut, which may cause disturbances of the normal flora resulting in alterations in the microbiome.

The use of vancomycin decreased from 2003 to 2013. One reason for this might be the extensive training given to prescribers on the appropriate use of vancomycin [138]. Empiric misuse of vancomycin in staphylococcal infections is relatively common, despite the fact that MRSA infections were very rare at the Children's Hospital. MRSE infections, on the other hand, were relatively frequent, but these infections rarely require vancomycin initially. Another reason for the decline in the consumption of vancomycin may be the increased consumption of teicoplanin. The consumption of vancomycin and teicoplanin in DDDs cannot, however, be compared by using DDDs. Teicoplanin was more often prescribed for older children with malignancies, whereas vancomycin was more frequently given to patients in neonatal units.

The overall consumption of antifungals decreased somewhat during the study period. Novel antifungals were rapidly adapted into clinical use despite lack of data on their safety and efficacy [139]. The most frequently used antifungal was fluconazole, followed by caspofungin and amphotericin B (mostly liposomal). However, the use of both amphotericin B and fluconazole decreased over the years and these antifungals were replaced by novel azoles (voriconazole and posaconazole) and echinocandins (caspofungin and micafungin). These drugs are costly compared to azoles and amphotericin; however, data suggest that they may be safer for children than conventional therapies for candidaemia [139–143]. When further developing prudent use of antimicrobials at the Children's Hospital, the cost-benefit analysis of new expensive therapies can be likewise implemented to an ASP.

Regarding the use of antivirals, the total consumption of valganciclovir was the greatest, followed by siddofvir and tsanamavir. The use of aciclovir, valaciclovir and valganciclovir has increased, whereas the use of ganciclovir has decreased. In Europe, the use of antivirals has varied greatly mainly because of the use of HIV/AIDS drugs [144]. In Finland, the prevalence of HIV is very low and therefore consumption of anti-HIV medications is minimal [145].

Defined daily doses were used for measuring antimicrobial consumption in children. Although the DDDs are definitely not ideal for measuring consumption of antimicrobials in children, Study II was able to describe how the consumption of

different antimicrobials has changed from 2003 to 2013 in this tertiary children's hospital. Thus, despite the shortcomings of this method, it allows us to compare temporal trends in a single hospital. DDDs are used in other children's hospitals as well when investigating the consumption of drugs [146–149]. Similarly, a study by Wu *et al.* demonstrated that monitoring consumption of antimicrobials by using DDDs reduces their unnecessary use and resistance [150]. Hence, a culture-guided de-escalation of antimicrobials is an effective element of an ASP. The strength of Study II was the large amount of material covering the consumption of all antimicrobials used in the Children's Hospital during a period of 11 years. This long surveillance period gives good insight into the consumption of antimicrobials in a tertiary care hospital in a country with a relatively low number of multiresistant bacteria such as MRSA and ESBL.

Study II cannot be directly compared to other hospitals with different patient profiles. Similarly, the consumption of these pharmaceuticals cannot necessarily be compared to countries where multiresistant bacteria are more frequent. Likewise, guidelines for antimicrobial use can differ from country to country. In addition, the choice and dosing of an antimicrobial for a certain infection can vary. As well, in children, the quantification of consumption by using DDDs is not as precise as that of adults. Therefore, the consumption of different antimicrobials cannot be directly compared since the DDDs vary greatly between different drugs. Also, if the use of one antimicrobial is reduced in the neonatal ward, it will most likely not be seen in DDD figures since the dose of antimicrobial for neonate is so much smaller compared to one DDD, which is the recommended daily consumption for an adult [151,152]. Hence, if the same use of the drug is reduced in a ward that takes care of primarily adolescent patients, it will be seen in decreased DDDs.

Finally, to further estimate the consumption and rational use of antimicrobials, more data, such as prescription data, indications and the ages of the children, are needed to evaluate the trends in the use of different antimicrobials. Benchmarking to other hospitals nationally regarding antimicrobial consumption and policy is not as informative as comparing the Children's Hospital with other tertiary paediatric hospitals in Nordic countries with similar patient profiles would be. In general, the AMT given at Helsinki's Children's Hospital is more complex compared to other paediatric hospitals in Finland. The Children's Hospital, HUCH, is the only hospital with paediatric patients with complex oncology and stem cell transplantations, organ transplant, open heart surgery and other demanding surgeries. Seeking appropriate AMT policies can be done by comparing the Children's Hospital to other Nordic countries and by utilizing tools and information provided, for example, by GARPEC (Global Antimicrobial Resistance, Prescribing, and Efficacy among Neonates and Children) [153]. The GARPEC project is a global surveillance network focused on collection of data on neonatal and paediatric antimicrobial prescribing and resistance.

6.3. OFF-LABEL USE OF ANTIMICROBIALS (III)

Study III consisted of three separate studies investigating OL use in children (Table 9.). The main finding of Study III was that one-fifth of premature neonates weighing 400–2000g with blood culture positive infections received at least one antimicrobial OL (51/282). Study III shows a correlation between weight and the use of OL antimicrobials. An increase in birth weight was found to statistically significantly decrease the probability of OL usage.

In the second study, included in Study III, of 282 premature neonates, 16% were given meropenem. Despite the OL status of meropenem, it has been found to be safe and effective in infants [155]. In addition, many studies have been published on appropriate dosing regimens of meropenem in neonates [154–158]. At present, there is an ongoing process (NEOMERO research) to provide data for the authorisation of meropenem in neonates [159]. Meropenem is widely used in NICUs, and clinical experience suggests that it is safe to use in neonates. Lack of market authorisation may be due to the absence of a pharmaceutical company or research group to analyse available data and compile recommendations.

In the second study of Study II, 3% of premature neonates were given rifampicin despite its OL status. Rifampicin has been on the market for decades, but very few studies on the use of rifampicin in combination with other antimicrobials in premature neonates [160–162] have been published. Taken together, the present data on rifampicin pharmacokinetics in neonates are insufficient [163], and it is unlikely that its OL status will change in the near future.

A few premature neonates in Study III were given parenteral ciprofloxacin OL. Ciprofloxacin has been shown to be a rare cause of adverse musculoskeletal effects in children [164]. The safety of ciprofloxacin has been studied with favourable results in full-term and premature neonates [165–166]. The follow-up periods of the treated patients for safety have, however, been relatively short—only one or two years.

Among the 282 premature neonates, one was treated with caspofungin. For decades, amphotericin B and fluconazole have been the first-line antifungal therapies in severe fungal infections, having only recently been replaced by novel antifungals. Compared with amphotericin B, caspofungin seems to cause less adverse reactions in neonates with candidaemia [169], and it seems to be well tolerated and effective in premature and full-term neonates and older children [170–173].

As the examples discussed above indicate, OL status does not necessarily mean that the drug is not safe and effective to use in neonates or children. Research data related to dose, efficacy and safety may be available but have not been submitted to regulatory authorities for labelling. Age-appropriate dosing recommendations for children may be found for some commonly used drugs not labelled for children in formularies like BNFC (British National Formulary for Children), and databases such

as Micromedex^R (US). These recommendations are given by clinical professionals and the recommendations are based on academic research and clinical experience. However, there are often no clear and exact recommendations for the youngest age group, like the premature neonates. Many antimicrobials used OL have established their place in the management of infectious diseases in neonates. Despite recent positive development in paediatric research, efforts are still needed, particularly regarding data on dosing and pharmacokinetics [2].

In addition to new drugs, many antimicrobials that have been on the market for decades are not labelled for children of all ages and particularly not for neonates. In the Children's Hospital's NICU during the study period, 35% of the most frequently used antibacterials were used OL. The risks of OL use in neonates clearly outnumber the risks for older children [9, 10, 174]. Neonates, particularly premature, may be more prone to adverse effects of drugs due to their undeveloped organ systems. Systematic literature review on drug use in NICUs conducted by Krzyżaniak *et al.* concluded that safety concerns regarding drug use in neonates include high use of antibiotics and OL and unlicensed medicines. Likewise, especially for neonates, it is not only the lack of data concerning the active drug, but also that of the excipients that need to be gathered for safety and efficacy [176]. Quality, safety and efficacy of AMT are also essential elements of ASPs. Hence, investigating and auditing of OL drug use should be included in a paediatric hospital's ASP.

6.4. ANTIMICROBIAL MEDICATION ERRORS (IV)

More than half of the errors in Study IV occurred with beta-lactams (84/157, 54%), which are the most consumed antimicrobials at the Children's Hospital. This study demonstrates that many antimicrobial errors occur due to the large consumption of these drugs in use at the Children's Hospital [123]. The results suggest that, in general, there are no drug-specific errors and the safety of AMT can be presumed to be of good quality.

In this study, the drugs with the most commonly reported errors were related to use of cefuroxime (15/157, 10%), penicillin G (15/157, 10%), vancomycin (13/157, 8%), netilmicin (12/157, 8%) and amoxicillin (12/157, 8%). Fluconazole was the most commonly reported antifungal involved in all antimicrobial errors (5/157, 7%). This finding was not surprising since these drugs are also the most frequently used drugs in the Children's Hospital [123]. These results are mostly in line with literature. Antibiotics commonly involved in medication errors in neonates have been amikacin [177], benzylpenicillin [178], gentamicin [177–179], vancomycin [177, 178] and piperacillin tazobactam [178], whereas in older children the medications are penicillin G [180] and gentamicin [180].

Most of the errors occurred with parenteral administered antimicrobials. The most common error types for intravenous administration were wrong dose/dosing interval, preparation of the drug prior to administration and omission (Table 16.). The most common error types for orally administered antimicrobials were omission, wrong dose/dosing interval and prescription. It is notable that omission errors occur often with both intravenously and orally administered drugs. Omission error was the most common error type regarding parenteral administration in GEN and INF wards and regarding oral administration in GEN, HEM-ONC and INF wards. Based on Study IV, an omission error was a typical error occurring with antimicrobials. The data show that 25% (37/149) of all errors were omission errors, whereas in other studies, not focused only on antibiotics, the prevalence of omission errors was lower at 12–23% [23, 26, 33]. This is an interesting finding and suggests that omission errors occur more often with antimicrobials. Compared to many other drugs in use at hospitals, most antibiotics are administered several times a day, which may increase the risk of staff forgetting to administer them.

Medication errors are common among cephalosporins because the generic names of these drugs are very similar to each other (such as ceftazidime, ceftriaxone and cefuroxime). Hence, these drugs are well-known look-alike and sound-alike (LASA) medicines [181]. In Study IV, 5 patients (5/149, 4%) received a cephalosporin different from that which was prescribed. This may be due to the similar names of the drugs and also because the drugs are stored close to each other. Usually no major clinical harm took place after these errors. The antibiotic spectrum of these drugs is different, however, and using, for example, cefuroxime instead of ceftazidime in treating an infection caused by *Pseudomonas* species may be harmful. Hence, if medicine cabinets are organized by the active substance in alphabetical order, all cephalosporins are located next to each other. On the other hand, using generic names of the drugs clearly increases safety when compared with trade names. According to the Institute for Safe Medication Practices (ISMP), TallMan letters can be used in order to separate different cephalosporins from each other [182]. On the other hand, a large-scale study conducted in 42 US hospitals revealed that the use of TallMan letters did not prevent LASA medication errors [183].

In Study IV, 24% of errors were dose-related (36/149). A total of 3% (4/149) of patients received a double dose of oral amoxicillin (Table 17.). However, the consequence of such an error is not serious. The most likely consequence for the patient receiving too high a dose of antibiotic is loose stools and diarrhoea. Sometimes too high a dose may be more harmful. For example, a study investigating overdose of drugs that require renal dose adjustments discovered that of the 20 most commonly overdosed drugs, 65% were antimicrobials (13/20) and one of those drugs was amoxicillin [184].

In Study IV, only two patients experienced clinically serious antimicrobial errors (2/149, 1%), i.e., overdosing of vancomycin and teicoplanin. Antimicrobial errors

are, fortunately, not often clinically significant as can be seen in this study. The findings are in accordance with other studies investigating medication errors in children, which found that clinically significant errors are rare [24, 25, 30].

In general, antimicrobials do not result in clinically significant adverse effects such as other drugs like opioids or cytotoxics. However, some errors, such as the ten-fold errors, are potentially dangerous to children and especially to neonates. Ten-fold errors in dose are well-known errors in paediatrics [185]. Ten-fold errors may easily occur when drugs are prepared for children from drug products aimed at adults. Hence, prior to administration to children, the drugs often need dilution to prepare a suitable dose and administration route for paediatric patients. Ten-fold errors were, however, not commonly recorded in Study IV. There was only one ten-fold error that reached the patient: a premature infant received a dose of vancomycin ten times too high. The outcome was favourable, and no irreversible side effects developed.

Overall, neonates experience the same types of errors as older children. They are, however, more prone to errors due to more complex preparation and administration phases of the drugs [177, 186]. Likewise, the pharmacokinetics and dynamics of the drugs are often not well known in children, especially in neonates [186]. These issues expose neonates more often to administration and dosing errors.

Human factors contribute to medication errors. The times of shift changes of nurses are potentially hazardous periods of time to forget to administer antimicrobials, leading to an omission error. The most frequently reported primary causes for omission errors were related to environment, equipment and resources (10/31, 32%). There were altogether 66 administration errors (63%, 66/105) reported from GEN, HEM-ONC and INF. Out of those, 18% of reports stated that there were no special circumstances contributing to the error and that the situation was normal when the error occurred (12/66, 18%). This finding highlights the fact that no matter what the circumstances are, errors do occur. This is why it is particularly important to develop protective measures that cover all circumstances. Several free comments were also given by the persons who reported errors. In these comments, the following root causes for errors in GEN, HEM-ONC and INF were given: being busy, different practices in different wards, often changing staff, not enough knowledge or education, too many patients/nurse and many patients with difficult co-morbidities.

The number of error reports has increased over the years in the Children's Hospital, and the use of the HaiPro tool is constantly increasing. This increase is most likely due to increased awareness of the HaiPro system and promotion of a blame-free atmosphere regarding errors occurring at the hospital. However, the reporting activity has not yet reached a plateau and errors remain under reported (Figure 14.).

Medical doctors submitted only 3% of antimicrobial error reports. This is very concerning, and they should be actively educated about the benefits of the reporting system and their reporting should be also followed. Although medical doctors did not prepare and administer the drugs, they prescribed the drugs and if the prescription were inappropriate, e.g., an inappropriate dose, it could lead to a medication error that reaches the patient. The lesser activity of medical doctors might be explained by their role as prescribers. The consulting doctor may never hear about a patient after prescribing a drug unless a problem occurs with the therapy. Hence, the doctors may not be eager to report identified errors due to lack of understanding of the workflow leading to a medication error. Even though the prescription might be appropriate (e.g., correct drug, correct patient, correct dose, correct administration route), errors can occur. For example, if the prescription itself was not clear and accurate for the nurse administering the drug, an error can occur. Communication is challenging in all work environments, and special emphasis should be placed on communication when training staff. Currently, medical doctors receive feedback from obvious prescription errors, such as too high a dose of a drug or a wrong drug prescribed, but less obvious errors are perhaps not easily spotted by the healthcare staff.

Most of the reported errors reached the patient (84%). This indicates that healthcare professionals at the Children's Hospital mainly report on errors that reached the patient. Reporting of near miss errors is also important because if only the errors reaching the patients are being reported, it will be increasingly challenging to prevent errors if there are not sufficient data regarding near miss cases. In Study IV, HEM-ONC reported more near miss errors than other wards. This might be due to more potent and toxic drugs in use in HEM-ONC compared to other wards. Hence, in general, the consequences in HEM-ONC may be more severe for the patient if medication error occurs. Healthcare workers see the importance of reporting near miss errors in HEM-ONC in order to create protective measures.

While there were only two clinically significant antimicrobial errors, these results suggest that the following issues should be addressed at the hospital in order to further improve safe and effective antimicrobial therapy and promote a culture of medication safety: encourage medical doctors' activity in reporting errors, encourage all healthcare professionals to report near miss errors more often, provide nurses with sufficient time without distractions when preparing or administering drugs, unify practices between all wards (there should not be different practices between different wards inside the same hospital) and add more clinical pharmacists to the multidisciplinary team. Clinical pharmacists in wards decrease medication errors [177].

An ASP is valuable in reducing antimicrobial prescription errors, for example [187]. Manias *et al.* investigated which types of interventions helped to reduce medication errors in paediatric intensive care [188]. They discovered that the

following interventions reduced medication errors: computerized medical doctor order entry, intravenous systems, education modes, protocols and guidelines, clinical pharmacist involvement and support systems for clinical decision making. Few studies have investigated digital programs reducing medication errors, including electronic trigger detection tools that can detect overdoses of antibiotic [189] and electronic medication reconciliation at discharge stage [190]. These types of programs could also be useful at the Children's Hospital.

6.5. STRENGTHS AND LIMITATIONS OF THE STUDIES I-IV

There were several limitations in Study I. First, Study I was retrospective and it was possible to collect only data that were recorded. Second, the number of patients in this study was relatively small and therefore general assumptions regarding the overall occurrence of true faults were difficult to calculate. Third, the antimicrobials used were evaluated by an expert panel. Thus, the classification (appropriate vs. inappropriate) was of course a subjective opinion of the panel. The evaluation was, however, based on microbiological *in vitro* data. Fourth, the pathogens isolated from the blood cultures may not always represent the sole pathogen that causes the infection. Hence, sometimes the care-provider may be reluctant to de-escalate the chosen antibacterial therapy when the blood culture shows growth of a single pathogen. This may result in treating children with severe underlying conditions with broad-spectrum drugs ("just in case").

Regarding Study II, the DDDs are not an ideal measurement of drug use in children. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults [95, 96]. However, as long as paediatric DDDs are lacking, DDDs may be used to describe paediatric consumption of individual antimicrobials over a certain period of time in a setting where no major changes in the hospital patient population takes place. A novel, more accurate method of evaluating paediatric drug use is, however, urgently needed.

There are several limitations in Study III. Since the data were collected from a single hospital, the sample size was relatively small. However, the main finding of Study III regarding the relatively frequent use of OL antimicrobials, especially among neonates, is universal and concerns most NICUs. The retrospective nature of the study created difficulties in data collection. The results of Study III underestimate the true OL use of antimicrobials in neonates, as in order to comprehensively evaluate the prevalence of off-label use, dose and indication should be identified in addition to the age of the patient. In Study III, the data regarding the doses and dosing of antimicrobials for premature infants could not be collected because the electronic records mainly did not enable this.

Data from Study IV were from a single institution, and results cannot be generalized to other environments. However, many common aspects were discovered with the existing literature. In Study IV, the number of medication errors included was relatively small; however, the data were collected throughout the period available for electronic medication errors.

6.6. RECOMMENDATIONS AND CLINICAL IMPACT OF STUDIES I-IV

The use of antimicrobials in children was evaluated in four studies. The results from the Studies I–IV are summarized and follow-up at the Children’s Hospital shown in Table 18. So far, education of healthcare staff has been a main measure supporting the rational use of antimicrobials. This thesis has also triggered a few studies regarding appropriate use of AMT at the Children’s Hospital.

Table 18. Summary of Studies I-IV and follow-up at the Children's Hospital. AMT=antimicrobial therapy, OL=off-label, ASP=antimicrobial stewardship program.

| Study | Focus of the study | Core elements of studies related to ASPs | Main findings | How the Children's Hospital has used the results |
|------------|--|---|--|---|
| I | Appropriateness and quality of AMT for blood culture positive infections | <ul style="list-style-type: none"> antimicrobial resistance use of broad spectrum antimicrobials quality and safety of care adverse effects | <ul style="list-style-type: none"> more attention should be paid to appropriate use of antimicrobials in order to guarantee effective treatment training of prescribers should be urgently provided | <ul style="list-style-type: none"> training of doctors regarding prescribing of antimicrobials and de-escalating of AMT and reacting on laboratory results |
| II | Consumption of antimicrobials in The Children's Hospital | <ul style="list-style-type: none"> antimicrobial resistance consumption of antimicrobials use of broad spectrum antimicrobials | <ul style="list-style-type: none"> the use of carbapenems has increased significantly during 11 years the resistance of <i>Pseudomonas aeruginosa</i> against different antimicrobials has increased rapidly | <ul style="list-style-type: none"> training of junior doctors regarding prescribing of broad spectrum antimicrobials paying more attention overall to the prescription of broad spectrum antimicrobials |
| III | Prevalence of OL use of antimicrobials in neonates | <ul style="list-style-type: none"> consumption of antimicrobials quality and safety of care adverse effects | <ul style="list-style-type: none"> off-label use of antimicrobials was most common in premature neonates the less weight premature neonates (400-2000g) had, the more likely they were receiving OL antimicrobials | <ul style="list-style-type: none"> notifying authorities |
| IV | Prevalence and quality of medication errors occurred with antimicrobials | <ul style="list-style-type: none"> quality and safety of care adverse effects | <ul style="list-style-type: none"> antimicrobials most commonly associated with errors were likewise antimicrobials most often consumed at the hospital most common error type was administration errors and 1/4 errors were omission errors | <ul style="list-style-type: none"> training of healthcare staff regarding typical errors and how to avoid them training medical doctors to report prescription and other identified errors |

6.7. ANTIMICROBIAL THERAPY IN THE CHILDREN'S HOSPITAL AND RECOMMENDATIONS FOR ANTIMICROBIAL STEWARDSHIP PROGRAM

There are five tertiary university paediatric hospitals in Finland. The Children's Hospital, HUCH, is the only hospital with paediatric patients with complex oncology therapies and stem cell transplantations, organ transplant, open heart surgery and other demanding surgeries. Hence, the antimicrobial therapy in Helsinki's Children's Hospital is more complex compared to other paediatric hospitals in Finland. Comparing the five children's hospitals is relatively difficult since there is significant diversity among them.

At the moment, there is no official ASP at the Children's Hospital. Use of antimicrobials is controlled and monitored in passive ways such as education of staff, follow-up on consumption of antimicrobials and resistance rates at the hospital. At the Children's Hospital, the HUS-pharmacy delivers data on consumption of antimicrobials twice a year to the infectious diseases consultants. These data include drug consumption according to medical ward. Currently, there are four infectious diseases consultants working at the hospital.

Even though the Children's Hospital is a relatively small hospital, more active measures are recommended in order to ensure more prudent use of antimicrobials. Currently, there is ongoing research regarding antimicrobial prophylaxis prior to surgery. The duration of AMT, such as prophylaxis for surgery or AMT for infection, is important to monitor. The duration of AMT should be more investigated. Auditing the quality, safety and efficacy of AMT conducted in individual patients is of high importance as well. Currently the indications of prescribed antimicrobials are audited four times a year. Regarding antimicrobial resistance, a few broad-spectrum antimicrobials could have limited prescription rights and in these cases, a general practitioner should always consult an infectious diseases specialist.

Currently, electronic systems for patient data are under development in Finland. Epic (in Finland called Apotti), an extensive change project of the social services and healthcare field, will unify digital patient data between hospitals operating in the Finland area (HUS area) [191]. In the Children's Hospital, measures of building a trigger tool for medical doctors prescribing antimicrobials is under consideration related to Apotti. When prescribing antimicrobials, there could be an obligatory "questionnaire" for every antimicrobial course prescribed. The prescriber would document if the AMT is empirical or targeted, what the indication is and the expected duration of therapy in days. These kinds of useful electronic tools are also introduced by two studies [189, 190]. Overall, enhanced real-time communication among different healthcare professionals such as prescribers, nurses, clinical microbiologists and clinical pharmacists could be supported via Apotti.

Systematic review by Schuts *et al.* offers an evidence-based list of key measures assuring the prudent use of antimicrobials. This list includes five core elements: 1) empirical treatment according to local or national guidelines, 2) de-escalation of treatment, 3) parenteral-to-oral switch, 4) therapeutic drug monitoring and 5) restricted antimicrobial lists [90]. The current use of these measures and proposed new measures at the Children's Hospital can be seen in Table 19. These five core elements have an effect on clinical outcome, adverse events, treatment costs and antibiotic resistance rates. Regarding parenteral to oral switch, clinical pharmacists have knowledge on switching highly bioavailable antimicrobials from the intravenous route to the oral route for patients who are good candidates [192]. These antimicrobials include, for example, quinolones, metronidazole, macrolides, doxycycline, clindamycin, rifampicin, linezolid and fluconazole. The efficacy of oral administration of these antimicrobials is almost equivalent to the efficacy of the intravenous route.

Recommendations regarding prudent use of antimicrobials, research and ASP at the Children's Hospital are introduced in Table 20. Establishing a coordinated and systematic ASP for the Children's Hospital is supported by many studies conducted in paediatric hospitals [125, 187, 193–196]. Annual audits of antimicrobial consumption and evaluation of the appropriateness of AMT for different indications and patient groups should be conducted regularly. Moreover, involving a clinical pharmacist (specialized in infectious diseases) on the ASP team would be beneficial according to many studies [197–200]. Pharmacists trained in infectious diseases can also coordinate an ASP and conduct interventions and audits independently [201].

Table 19. Current situation regarding prudent use of antimicrobials and recommended next steps for further supporting judicious use of antimicrobials and launching of ASP at the Children's Hospital.

| Issue | Issue identified or investigated by this thesis | Issue currently monitored regularly at CH | Tool(s) currently in use at CH | Possible current problems identified by this thesis or reported by healthcare staff | Proposed next steps or tool(s) |
|--|---|---|--|---|--|
| 1) Prescribing empirical AMT according to local guidelines | yes | yes | Medical wards have their own recommendations on AMT for different indications | There are different recommendations in different wards inside the hospital | Offering guidance on appropriate prescribing by using electronic trigger tools |
| 2) De-escalation of AMT if necessary | yes | partly | Prescribers are educated regularly on the appropriate prescribing and antimicrobial resistance | De-escalation does not occur enough and appropriately | Regular audits and further education of prescribing (junior) medical doctors |
| 3) Parenteral to oral switch | no | no | No specific tools, used drugs and administration routes are recorded electronically | Switch is not "centrally" monitored | Research/audits regarding switch (such as with quinolones, metronidazole, macrolides, doxycycline, clindamycin, rifampicin, linezolid and fluconazole) and education of healthcare staff and involving a clinical pharmacist |
| 4) TDM | partly | no | Conducted TDM is recorded electronically | There is a great deal of inappropriately conducted TDM such as forgetting to take a sample or taking samples at inappropriate times | Research/audits regarding TDM (such as in glycopeptides and aminoglycosides) and education of healthcare staff |
| 5) Restricted antimicrobials list | no | no | There is no list on restricted antimicrobials | Somewhat varying prescribing patterns depending on the prescribers | List of restricted antimicrobials (such as linezolid) and implementation of restricted antimicrobial policy generated by experts |

CH=Children's Hospital, AMT=antimicrobial therapy, TDM=therapeutic drug monitoring, ASP=antimicrobial stewardship program

Table 20. Recommendations for the Children’s Hospital based on this thesis.

| Practical recommendations |
|--|
| <ul style="list-style-type: none"> • Establishing a coordinated and systematic ASP for the Children’s Hospital • Establishing a new position for infectious diseases pharmacist for HUS area – the infectious diseases pharmacist can be consulted by the Children’s Hospital as well • Creating new electronic tools for assuring the prudent use of antimicrobials by offering guidance on appropriate prescribing and trigger tools related to prescribing, monitoring of prescribed antimicrobials and enabling trigger tools for identifying risk factors of AMT in children |
| Research recommendations |
| <ul style="list-style-type: none"> • Establishing a research group consisting of medical doctors, nurses, clinical microbiologists and clinical pharmacists to conduct benchmarking from other Nordic tertiary paediatric hospitals and implementation of an ASP particularly designed for Children’s Hospital • Research and audits regarding the quality, safety and efficacy of AMT with different paediatric patient groups and indications • Retrospective audits regarding TDM taken with antimicrobials requiring TDM • Research regarding restricted antimicrobials in Nordic countries and, if required, implementation of “restricted antimicrobials” list • Research regarding the current practices on parenteral to oral switch with AMT • Investigation on how the co-operation of HUS-pharmacy and Children’s Hospital could be further supported and enforced regarding implementation of ASP to the Children’s Hospital |

ASP=antimicrobial stewardship program, AMT=antimicrobial therapy, TDM=therapeutic drug monitoring, HUS=Hospital District of Helsinki and Uusimaa

6.8. FUTURE CONSIDERATIONS

Based on Studies I–IV, there are numerous suggestions for further studies. First, the quality of AMT in BSIs is an area lacking in information on children. Therefore, related to Study I, it is reasonable to recommend research and audits for other paediatric hospitals treating BSI patients and patients with other hospital infections such as (other) post-surgery infections. Severe or fatal harm may result for the patients whose hospital infections are undertreated, i.e., blood culture results should be acted upon accordingly at all times. If, after approximately 48 hours from the diagnosis of BSI, the decision regarding appropriate targeted AMT is not re-evaluated against the empirical AMT, this is alarming. In some hospitals abroad, such as in the UK and US, clinical pharmacists are conducting regular audits regarding appropriate use of antimicrobials [199, 202]. Pharmacists are able to compare the conducted AMT to local guidance or national policies. A retrospective study regarding the impact of evaluation on AMT conducted by clinical pharmacists

should be performed in Finland. This study would investigate the possible role of pharmacists in these types of tasks. This study would aid the co-operation between different healthcare professionals and strengthen co-operation between infectious disease consultants and clinical pharmacists working in medical wards or at hospital pharmacies.

Second, all factors that compromise paediatric AMT safety should be targeted for further research, including OL use of antimicrobials, especially in premature neonates, and antimicrobial medication errors. In Study III, it was discovered that OL use of antimicrobials is common in neonates. Further studies should be conducted about the correct dosing of these drugs to this vulnerable patient group. Doses from adults cannot always be extrapolated for neonates according to weight or other parameters. In addition, children are prone to different kinds of medication errors compared to adults. A typical example is ten-fold errors regarding dosing. Hence, it would be important to further investigate antimicrobial errors in paediatrics. These errors are not likely to cause significant risk for the patient, but due to the large volume of these drugs in use, it is important to invest in safe AMT. Study IV demonstrated that two clinically significant errors occurred with antimicrobials, both with renal toxic antimicrobials (vancomycin and teicoplanin). Hence, these groups of antimicrobials with the potency to cause severe harm if used inappropriately, should be specifically targeted in future studies. Also, it was discovered that when preparing drugs for children from products aimed at adults, the process can cause significant risks possibly leading to medication errors. Therefore, the preparation phase of antimicrobials, such as a nurse or pharmacist diluting a drug for a child before administering it, should be targeted for research in order to create safety warnings for healthcare workers preparing antimicrobials for administration at hospitals or at other facilities.

Third, antimicrobial resistance is a future global threat. It is important to perform regular surveillance on the antimicrobials used in hospitals in order to gather information nationally and globally to further evaluate the situation and create accurate local protocols to reserve broad-spectrum antimicrobials for cases where they are the only drugs working against resistant pathogens. For example, in Study II, an alarming increase was discovered in the use of carbapenems in the Children's Hospital. It would be valuable to investigate the situation in other children's hospitals in Finland and create a national surveillance method for antimicrobial consumption in children.

Future research regarding prudent use of antimicrobials in the Children's Hospital and establishing a coordinated and systematic ASP to the Children's Hospital is introduced in Table 20. The cost-effectiveness of different types of measures relating to ASP should be researched and evaluated prior to implementation.

7. CONCLUSIONS

The conclusions of Studies I–IV are the following:

1. Surprisingly, many patients received inappropriate AMT for BSI. Despite the relatively high number of inappropriate AMT given, only three cases were directly harmful to the patient who did not receive effective AMT for BSI. However, suboptimal therapy of, for example, staphylococcal infections was not uncommon. No patient died due to this, and overall the mortality was low compared to international studies with paediatric BSI patients.
2. Increased use of carbapenems during 11 years of surveillance was the most significant finding. This finding is in line with other European hospitals and should be evaluated carefully since the selective pressure caused by these drugs is a potential threat. The year-over-year consumption of antibacterials was in general relatively stable and new antibacterials were put into use conservatively. In contrast to antibacterials, novel antifungals were rapidly adopted into use despite scarce evidence of their safety in children.
3. Off-label use of antimicrobials according to age was surprisingly low in the point prevalence study in children 0–17 years old. The prevalence of such use is more prominent in preterm and full-term neonates and is more likely the lower the neonate's birth weight is at the time of antimicrobial therapy. More studies in neonates, particularly regarding dosing and pharmacokinetics of antimicrobials, are urgently needed.
4. Reports from antimicrobial medications given in the inpatient services over 5 years have shown a minimal predilection for specific groups being high risk. No significant antimicrobial medication errors reported via HaiPro regarding specific antimicrobials were found. Both system-based high reliability safeguards as well as human factors solutions will continue to be important. Medical doctors should be further educated and informed about the importance of reporting medication errors. More good quality studies, with large enough data, are needed in order to determine the most efficient interventions to prevent antimicrobial errors in paediatrics.

The main conclusions from each of the Studies (I–IV) have been used to improve and develop current practices mainly by educating healthcare professionals regarding appropriate antimicrobial therapy and medication safety. The Children's Hospital

does not currently have an official ASP; however, this thesis has initiated projects regarding prudent use of antimicrobials and further launch of an ASP. Establishing a coordinated and systematic ASP for the Children's Hospital would be beneficial and supported by literature. The cost-effectiveness of different types of measures relating to ASP should be researched and evaluated prior to implementation.

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